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SYSTEM OF
PHYSIOLOGIC THERAPEUTICS

VOLUME XI

System of Physiologic Therapeutics

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A SYSTEM

OF

PHYSIOLOGIC THERAPEUTICS

A PRACTICAL EXPOSITION OF THE METHODS, OTHER THAN DRUG-GIVING, USEFUL FOR THE PREVENTION OF DISEASE AND IN THE TREATMENT OF THE SICK

EDITED BY

SOLOMON SOLIS COHEN, A.M., M.D.

PROFESSOR OF CLINICAL MEDICINE IN JEFFERSON MEDICAL COLLEGE; PHYSICIAN TO THE JEFFERSON MEDICAL COLLEGE HOSPITAL, AND TO THE PHILADELPHIA GENERAL, JEWISH, AND RUSH HOSPITALS, ETC.

VOLUME XI

SERUM THERAPY

BY JOSEPH McFARLAND, M.D.

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY IN THE MEDICO-CHIRURGICAL COLLEGE OF PHILADELPHIA

ORGANOTHERAPY

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RADIUM, THORIUM, AND RADIOACTIVITY

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COUNTERIRRITATION, EXTERNAL APPLICATIONS, BLOODLETTING

BY FREDERICK A. PACKARD, M.D.

LATE PHYSICIAN TO THE PENNSYLVANIA HOSPITAL

AN OUTLINE OF THE PRINCIPLES OF THERAPEUTICS WITH ESPECIAL REFERENCE TO PHYSIOLOGIC THERAPEUTICS

BY THE EDITOR

WITH ADDENDUM ON X-RAY THERAPY

AND

AN INDEX-DIGEST OF THE COMPLETE SYSTEM OF ELEVEN VOLUMES

Illustrated

PHILADELPHIA

P. BLAKISTON'S SON & CO.

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PREFACE

With this volume is brought to conclusion a work that has occupied the editor's thoughts for twenty years and has been under his hand almost constantly for the last five years.

In the prospectus of this System, the term 'Physiologic Therapeutics' was proposed with some hesitancy; but general adoption by writers has justified it and made it permanent. Meanwhile, the methods thus designated have been receiving increasing attention the world over. The development of radiotherapy has doubtless had much to do with this, but interest has by no means been confined to the one field; physiologic measures in general are occupying more and more space in current literature and in contemporary practice. That they will continue to grow in use and favor with physicians may confidently be predicted.

The present volume deals principally with subjects which, while they have not yet been worked out in full, give promise of large additions to our therapeutic armamentarium, and have indeed already furnished us —as in diphtheria antitoxin, in roentgenism and in thyroid and adrenal gland substances—with some of the most certain and most effective agents at our command.

The authors of the articles on Serum Therapy, Organotherapy and Radiotherapy have been conservative in their treatment of the themes assigned to them. While discussing all important matters with sufficient fulness, and permitting themselves occasional glances into the future, they have made no recommendation that has not been substantiated by the test of time; and they have excluded whatever seemed to possess ephemeral interest only.

In the short time since volume II was published, new light has been thrown on the constitution of matter, permitting a clearer view of the nature of electric phenomena; while from the side of practice, improvements have been made in the technic of Roentgen-ray applications and the scope of this important branch of Radiotherapy has become better defined. In the Addendum on X-ray Therapy, these recent advances in physical theory and therapeutic method have been summarized and the lines of future progress briefly indicated.

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Measures better known are considered in the articles on Venesection and Counterirritation. These expedients—at one time abused, but latterly too much neglected—have a definite field of usefulness, and it is a source of satisfaction to the editor to be able to present concerning them the judicious and well-tested views of his lamented friend, Frederick Packard.

The death of Dr. Packard is the only break that has occurred in the editorial and contributing staff of the System. It is little to say of that loveworthy and manly soul, that in Frederick Packard the world has lost one whose work, ever earnest, thorough and truth-seeking, had made him justly prominent among the younger leaders of medical thought; and from whose maturing powers and enlarging experience, enduring achievement was justly expected. As Dr. Packard's manuscript did not come into the editor's hands in time for the author to pass upon the advisability and acceptability of editorial suggestions, the few actual additions found necessary have been placed in brackets—a custom hitherto avoided.

Especial attention is directed to the INDEX-DIGEST OF THERAPEUTIC MEASURES, occupying 110 pages of this volume. Not even the editor had an adequate idea of the immense amount of labor that would be involved in its preparation. The mere handling of the numerous cards on which the basic memoranda were made, consumed in the aggregate no little time; while the hours needed to verify all the references, and make sure that there had been no serious omission, grew into days and weeks and months. The proofreading was scarcely less laborious, exacting and time-consuming. The delay in the appearance of this volume beyond the scheduled date is thus to be attributed entirely to the endeavor to make this important portion of the volume full and accurate.

It is the hope and confident expectation of the editor and the faithful and patient compilers that the Digest will prove of the highest usefulness. It is in effect a compendium of the practice of medicine from the viewpoint of treatment by physiologic measures; giving also many hints as to auxiliary treatment by drugs. In such matters as climates, lists of mineral springs, names of health resorts and the like it is not intended to be exhaustive; nevertheless it will be found to be richly suggestive. In other branches of the special subjects the endeavor has been to leave out nothing that might be helpful.

The Outline of Therapeutic Principles, reproduces in much condensed form the substance of several addresses on that subject delivered before medical societies and of a series of lectures introductory to the courses on Special Therapeutics at Jefferson Medical College (1887–1890) and on Materia Medica and Therapeutics at Dartmouth Medical College

(1890–1892), with certain additions in thought and illustration suggested by recent investigations in various departments of medical and general science. By a not unnatural reaction medical teaching to-day lays more stress upon laboratory investigation and bedside observation than upon instruction in theory. The importance of exact research and the necessity for teaching by example are beyond dispute. The pendulum has, however, swung too far. All medical practice is based upon theory —and the question is not between theory and no-theory, but between good theory and bad theory. Either treatment will rest upon the crude theory that a certain drug or measure is "good" for a certain symptom or group of symptoms, or there must be a critical analysis of the indications presented by the given case, and a judicious estimate of remedial means available. Intelligent analysis and deliberate choice of action (or inaction) are surely to be preferred to automatic routine or haphazard guesswork. If, moreover, analysis and action proceed from broad and comprehensive views based upon clear apprehension of fundamental principles, the better are likely to be both the underlying science that informs and the practical art that executes. Medicine is a department of biology, and not only pathology, but therapeutics also, must be studied in the light of general biologic knowledge, if enduring progress is to be made. In addition, basic relations with chemistry and physics must be sought and established. In the final application of principles to clinical conditions, experience must, however, continue to be the guide; and for this reason the wise maxims of the great masters of all ages must also be kept in mind and repeated to successive generations. Thus, while avoiding all attempts to establish restrictive and inelastic 'systems of healing,' we can nevertheless continue to systematize the principles of the healing art and to bring these into ever closer relation with the natural healing processes.

The editor takes this opportunity to thank the publishers and printers for their generous and hearty coöperation, and to express his acknowledgment of the faithful and scientific work of the contributors and editorial assistants. Acknowledgment is also made to the medical press for the generally appreciative and encouraging tone of reviews and criticisms; nor should there be omitted a word of heartfelt gratitude to the many physicians who have encouraged the progress of the work not only by their subscriptions but also by personal letters of approval.

One journal in its review of the System said: "The era of a broadly conceived therapeutics, which includes but by no means confines itself to drugs, has evidently dawned." It is the editor's highest wish to be able to believe that his work has been a contributing factor in this result.

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SERUM THERAPY

BY

JOSEPH McFARLAND, M.D.

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY IN THE MEDICO-CHIRURGICAL COLLEGE OF PHILADELPHIA

A SYSTEM OF PHYSIOLOGIC THERAPEUTICS

SERUM THERAPY

BY JOSEPH McFARLAND, M.D.

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CHAPTER I

THE EVOLUTION OF SERUM THERAPY

Historic: Phagocytosis; Serum Reactions; Agglutination; Precipitation; Hemolysis Cytolysis; Toxolysis.

Theories of Immunity: Metchnikoff's Theory of Phagocytosis; Ehrlich's Lateral-chain Theory; Natural Immunity; Immunization; Hemolysis and Bacteriolysis.

General Facts Regarding the Therapeutic Serums: Antitoxic Serums; Antimicrobic or Bacteriolytic Serums; Method of Immunization; Administration.

Definition

Serum therapy, or **specific serotherapy,** is an attempt to combat the activity of specific pathogenetic agents by specifically antagonistic substances contained in, or derived from, the cells and body-juices of animals artificially immunized against such infections. It is thus an outgrowth of **protective infection** and **protective intoxication.***

According to their method of production and action therapeutic

* It will be observed that this definition excludes the use of normally immune serums, which may hereafter play some part in therapeutics, as well as the use of various normal and artificially modified serums for other than specific purposes. These expedients, in so far as they are now or may hereafter become worthy of attention, pertain to the subject of *opotherapy*, or, more broadly, of *organotherapy*. It is, however, probable that in a region of investigation so recently entered upon many advances will be made and that our definition may have to be expanded accordingly.

serums—also called **immune serums** or **antiserums**—are divisible into two classes—**antimicrobic** and **antitoxic.** Neglect of this distinction has led to many errors in experimentation and in treatment.

In all bacterial diseases two classes of morbific effects are to be recognized: (*a*) tissue changes (inflammation, suppuration, necrosis, etc.), usually due to the actual presence *in situ* of the invading organism; (*b*) toxemia, due to poisons (soluble toxins), whether of intracellular or extracellular origin, with which the blood of the infected animal becomes charged as a result of bacterial activity. In certain diseases the lesion is prominent; in others the toxic action predominates. It is quite possible that serum therapy must be directed in accordance with these tendencies.

In our previous study of artificial immunity (see Volume V) the various methods of its production were set forth. Briefly summarized, they consist either in (*a*) the inoculation of attenuated living cultures of specific microörganisms, or in (*b*) the injection of the toxins (sterilized cultures, dead bodies and toxic filtrates) of such organisms; in both cases in progressively increasing strength or quantity. The resulting resistance to the specific infection is found to be associated with, if not dependent upon, certain properties of the blood serum of the immunized animals. These properties are manifested when the serum is mixed *in vitro* with the cultures or toxins of the specific microörganism employed, or injected into a susceptible animal after infection with that organism or intoxication with its dead substance or chemical products. Serum from an animal immunized by living cultures is active against living cultures; serum from an animal immunized by dead bacterial substance* or toxic filtrates is active against toxins. The former is, therefore, called a **bacteriolytic**† or **antimicrobic serum** or an **antimicrobin**; the latter, a **toxolytic** or **antitoxic serum** or an **antitoxin.**

The production of antimicrobins or antitoxins is but one manifestation of a general power of living organisms to protect themselves against hostile attack. It is a specific reaction to a specific action and must be considered in connection with many like phenomena. The chemical aspect of this power is receiving the greatest attention to-day, and for present purposes a chemical exposition will suffice. It will be

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* Dead bacterial (or other germ) substance stands midway between the living culture and the toxin, in the case of some organisms, at least. In the future it may be necessary to erect a third class to cover this distinction, but the classification here followed is simpler and for present purposes sufficient.

† Also **bactericidal** and **microbicidal** and **antibacterial serum.**

impossible without interfering with the logical presentation of the subject to describe all important experiments, or even to mention the names of all investigators; nor will a chronologic order be preserved.

Evolution of Serum Therapy

Scientific serum therapy is a very modern development, dating only from the researches of two Japanese savants, Ogata and Jasuhara, who in 1890 found that animals subcutaneously injected with blood drawn from animals immunized against anthrax likewise became immune. In the same year, and probably independently, Behring and Kitasato demonstrated the like facts for diphtheria and tetanus.

These brilliant results, however, depended upon previous researches and observations (see Volume V) of Metchnikoff, Pfeiffer, Buchner, Bordet, Salmon, Smith, Nuttall, Roux, Roser, Pasteur, Tyndall, Schwann, Jenner, Testy, Montagu and a host of other students and laymen. They are even foreshadowed in the lore and customs of savage tribes.

The facts important for us may most profitably be considered in summary under four heads: **agglutination, precipitation, cytolysis, toxolysis.** Two of these terms refer to reactions against living cells; two refer to reactions against poisons.

Agglutinins.—A very important field of knowledge, chiefly from the standpoint of the diagnostician, was Charrin and Roger's discovery of the agglutination of bacteria. In 1889, in the course of their studies on *Bacillus pyocyaneus*, these investigators observed what Gruber, Durham, Widal and Grünbaum erected into a method of diagnosticating typhoid fever and differentiating the typhoid bacillus from similar microörganisms. This agglutination of bacteria is a change resulting from the action upon the organisms or their appendages (Smith) of certain constituents of immune serums. When such serums are permitted to act upon cultures of bacteria, the motility of living cultures usually ceases, and the microörganisms, whether living or dead, aggregate in larger or smaller clusters, known as **agglutinins.** This reaction is not, as at present understood, one of immunity. Its exact nature is doubtful; but it has become extremely valuable, because it is distinctly specific; that is to say, the serum and body-juices of an animal infected with a certain microörganism exert this agglutinative action either upon that microörganism only, or to a much more marked degree upon it than upon its near relatives. Metchnikoff believes agglutination to be preliminary to some of the reactions of immunity, and its investigation is identified with the advance of the knowledge of immunity.

Precipitins.—Also important as illustrating the chemical nature of

some of the reactions of immunity is the discovery of the **specific precipitins** by Tschistowitsch and his followers. When animals are injected with certain substances, such as serum-albumins, egg-albumen or peptone, in less than toxic quantity, the blood serum of such animals will form precipitates when diluted and brought into contact with dilute solutions of the same substances, under the influence of time and warmth. These precipitates are specific. Serum modified through the stimulation of serum-albumin is inactive upon egg-albumen, and vice versâ; in the same manner that affected by the stimulation of repeated injections of peptone acts only upon peptone, and sometimes only upon the particular kind of peptone used in the experiment.

Cytolysis.—Since the days when the transfusion of blood was recommended as a therapeutic procedure it has been known that the heterogeneous corpuscles soon disappear, being dissolved or destroyed in some peculiar way. This question of **hemolysis** was subjected to thorough investigation by von Dungern, Ehrlich, Morgenroth and others, who found in the blood serums of animals repeatedly injected with heterogeneous blood certain **hemolytic factors** by which the destruction of the corpuscles is accomplished. These observations are of the utmost importance and show that the solution of blood-corpuscles is not a simple reaction, but is due to the combined effect of two distinct factors. One, called the **complement,** exists in slightly varying quantities in the blood of normal animals and cannot be materially influenced by experimental manipulation; the other, called the *immun Körper* or **immunizing body** (usually Englished "immune-body") is also present in varying quantities in the blood of normal animals, but is susceptible of great augmentation by experimental stimulation. The immunizing body is found to be stable, capable of resisting the effect of heat up to the coagulation-point for serum, and unaffected by ordinary influences. The complement, on the other hand, is labile, is readily destroyed by heat and is very sensitive to the effects of light and oxidation. Neither the immunizing body nor the complement is by itself capable of destroying the blood-corpuscles, but the combined action of these two factors rapidly brings about the solution. The reaction is specific because the immunizing body is specific; that is, a different reaction takes place in each case, depending upon the kind of foreign blood introduced to excite the formation of the immunizing body. So far as can be determined positively, the serum-complement is the same for all kinds of blood, though this point must be considered still unsettled.

The demonstration of the nature of hemolysis not only paved the way for an explanation of **bacteriolysis,** but incidentally disclosed a

group of reactions previously unsuspected; for it is now known that hemolysis is but one reaction of this kind, and that the introduction of various orders of cells stimulates the formation of specific immunizing bodies (amboceptors), capable, in the presence of a sufficient quantity of complementary substance, of bringing about the solution of the special cells that have excited their production. Thus the various **cytotoxins** (epitheliolysin, spermolysin, etc.) were discovered by Metchnikoff, Bordet, Gengou, Malvoz and a number of others. The knowledge of the conditions under which bacteriolysis takes place explains the comparative failure, thus far, of bacteriolytic serums in therapeutics, but may in the near future lead to the discovery of some method of rendering these substances available at the bedside.

Toxolysis.—In the body of an animal immunized against toxins specific neutralizing bodies—**toxolysins**—appear. They exert no effects upon the cells, but form inert compounds with such poisons as have stimulated their formation. They are usually known as *antitoxins*. Their action is direct, not intermediate, and their combinations with toxins resemble the chemical union of a base and an acid to form a salt.

Antitoxins and Bacteriolysins.—From the foregoing exposition the difference between the **antitoxic serum** and the **bacteriolytic serum** is seen to be quite great. The action of the former is direct and immediate, that of the latter, indirect or mediate, requiring the presence in the patient's blood of the necessary factors properly combined. The antitoxic serum is, therefore, immediately available for use in therapeutics; but the complicated reaction involved in the employment of the bacteriolytic serum makes its practical utilization difficult in the extreme.

THE MODERN THEORIES OF IMMUNITY FORMING THE SCIENTIFIC BASIS OF SERUM THERAPY

From the summary given in the foregoing pages it is evident that the facts constituting our knowledge of immunity and the various reactions associated with it have been gleaned one at a time and, for the most part, independently of one another. When first observed, they were inexplicable; the explanation came later, when the isolated facts were united into a comprehensive whole, chiefly by the genius of Ehrlich. In order that our view of serum therapy may cease to be that of an empiric application of scattered discoveries and that the method may at least seem to rest upon a substantial scientific foundation, it will be necessary to consider at greater length than in the study of prophylaxis (see Volume V) certain hypotheses recently advanced to explain im-

munity. These are Metchnikoff's modified hypotheses of "phagocytosis" and Ehrlich's "lateral-chain" hypothesis.

Phagocytosis

Metchnikoff's original conception, which gave to his theory its name, was that the infective agents of disease were actually devoured by the cells of the body, especially by the leukocytes of the blood, in the same way as the ameba devours the minute organisms upon which it feeds. It was soon shown by Buchner, Nuttall and others, however, that in many cases of immunity there is no visible phagocytosis, and that the body-juices alone, unaided by cells, possess the power of destroying bacteria. As the controversial point became more and more clearly proved, Metchnikoff, with wonderful ingenuity, accepted these observations and modified his theory to make it accord with them. In this modification the actual phagocytic or devouring process, at first the central element of the theory, has given way to a new conception.

How, says Metchnikoff, do the cells destroy the bacteria they incorporate but by **enzymes** contained within their cytoplasm and produced by their own synthetic processes? If these enzymes are in the cells and the cells take up the bacteria, the latter are destroyed within the cells by the enzymes. If the enzymes are liberated by the destruction of the cells (**phagolysis**), it is obvious that the tissue-juices which have taken up the products of cellular disintegration become endowed with the solvent powers originally possessed by the cells themselves. Thus Metchnikoff's phagocytosis no longer means the actual incorporation of the bacteria by the cells, but that all the reactions involved in the phenomena of immunity are referable to chemical products formed by, and commonly contained within, the cells and capable of acting upon the infective agents wherever they happen to meet. It will be observed that the hypothesis thus becomes a chemical one and that the destruction of bacteria is said to be effected by enzymes. It is believed that these enzymes destroy not only the bacteria, but their products as well, so that immunity may mean either destruction of bacteria or destruction of bacterial products.

Metchnikoff makes no distinction between the different classes of enzymes in these activities. He and his followers consider it probable that the same agent destroys the bacteria and neutralizes their products. Thus, the tendency of this hypothesis is to regard the phenomena of immunity as simple chemical reactions.

Not all the cells of the body are engaged in the defense of the organism against infective agents. Thus, Metchnikoff finds two classes of cells

active as phagocytes: the first group comprises the polymorphonuclear leukocytes of the blood and certain other similar cells, which produce an enzyme that he calls **microcytase.** Microcytase seems to attack bacteria; and **microphages,** as cells of this kind are called, develop their activity in infections of all kinds. Contrasting with these microphages are certain larger cells which Metchnikoff calls **macrophages.** The latter, which comprise the large mononuclear leukocytes, endothelial cells and certain connective-tissue cells, attack all foreign cells introduced into the body. Thus, blood-corpuscles introduced into the abdominal cavity are taken up largely by the endothelial cells of the peritoneum. The enzyme by which such cells are destroyed is called **macrocytase,** and all the so-called **cytotoxins** are viewed as closely related to, if not identical with, this enzyme.

To sum up this theory, immunity does not always depend upon the same fundamental reactions. It may depend upon the incorporation and destruction of bacteria by body-cells, or upon the destructive action of body-juices into which the cellular enzymes have been discharged; or, when microörganisms are not directly engaged in the production of disease and the morbid changes result from the presence of a toxin, as in diphtheria, tetanus and invenomation, immunity may depend upon the action of one of these enzymes on the poison introduced. According to this conception, therefore, diphtheria antitoxin must protect either through the action of cellular enzymes which it contains already formed, or by stimulating the formation of protecting enzymes within the body.

Lateral-chain Hypothesis of Immunity

Ehrlich's hypothesis is based on the mechanism of cellular nutrition, so that, as Welch has pointed out in his Huxley lecture on immunity, the two theories have this view-point in common. Ehrlich conceives the structure of protoplasm to be extremely complicated, and characterized by enormous numbers of lateral chains or groups of combining molecules—a conception borrowed from the structural diagrams of organic chemistry. These lateral chains—each being a definite molecular group—are supposed to have specific combining affinities. It is through the combination of particular molecular groups with appropriate groups in the tissue-juices that cellular nutrition and metabolism are supposed to be maintained. It is important to conceive of these groups as engaged in nutrition and as having each a specific affinity under normal conditions, in order to understand that what takes place under pathologic conditions through the production of peculiar

antibodies specific to the specific infectious diseases is, after all, but an exaggeration of the processes of health.

The circulating pabulum from which each cell of the body receives its nutrient factors is conceived by Ehrlich to be of a complexity even greater than that of the cells. It contains numerous molecular groups, each specifically adapted for combination with certain of the lateral chains of the various cells. As the needs of different cells vary, so their molecular lateral chains vary; and certain cells form combinations with molecular groups in the nutrient pabulum having no affinity for other cells. The lateral chains by which these combinations are formed have been called by Ehrlich **"receptors,"** and the appropriate molecular groups in the pabulum with which they combine, **"haptophores"** (ἅπτειν, to touch; φέρειν, to bring). It is quite probable that the haptophorous molecular groups habitually present in the normal body-juices are adapted for combination with the receptors of certain cells only. We can conceive that cells whose general characteristics and functions are similar may possess similar receptors, but that cells whose functions are peculiar and independent, such as the muscle-cells which contract, and the nerve-cells which originate impulses, must possess receptors peculiar to themselves (Fig. 1).

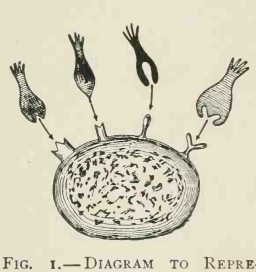

FIG. 1.—DIAGRAM TO REPRESENT THE CELL WITH ITS VARIOUS COMBINING GROUPS OR SIDE-CHAINS.—*After Ehrlich* (*Hewlett*).

Such being the conception of conditions in health, the way is paved for a similar conception of conditions in disease. In pathology we are obliged to consider the presence of abnormal substances in the body-juices. They may be of intrinsic origin, formed through perversion of metabolism, or, if extrinsic, may either be introduced from without or formed within the body as the products of foreign, and probably bacterial, energy. In either case, but particularly in the latter, new haptophorous molecular groups must be considered. According to the lateral-chain hypothesis, the ability of these substances to exert a deleterious effect upon the body depends upon their ability to attach themselves to the cell receptors. It is conceivable that many of these substances might have no proper adaptation by which this could take place; and it is also conceivable that, should such combination take place, it might be harmless, because the foreign haptophore might so closely resemble the normal haptophore as to perform the latter's

nutrient function. Again, the foreign haptophore may be capable of combining with certain receptors to which it attaches itself, and may injure the cell because it supplies no useful material and displaces that required by the cell. Finally, the foreign haptophore—and this is particularly so of the specific infectious diseases, especially diphtheria and tetanus—when it attaches itself to the appropriate receptor may not only displace the useful nutrient substances, but may be directly or indirectly injurious or destructive by means of an associated *toxophorous* group (toxic-complexus) (Fig. 2). Thus toxins are conceived to be

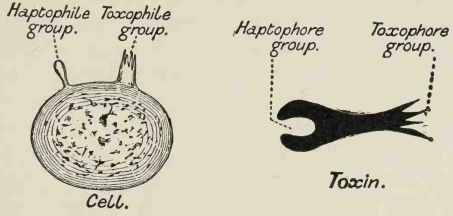

FIG. 2.—DIAGRAM TO REPRESENT THE COMBINING GROUPS OF THE CELL AND OF THE TOXIN RESPECTIVELY.—*After Ehrlich* (*Hewlett*).

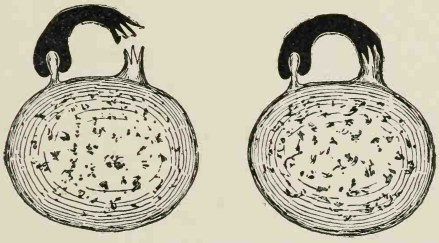

FIG. 3.—DIAGRAMMATIC SCHEME TO REPRESENT THE UNION OF TOXIN (BLACK) WITH THE CELL.—*After Ehrlich* (*Hewlett*).

complex, being composed of *fixation* (haptophorous) *groups* and *poisonous* (toxophorous) *groups;* while the cell is conceived to furnish appropriate receptor (*haptophilous* and *toxophilous*) groups through which the respective combinations are effected (Fig. 3). It is an element of the hypothesis that until the haptophore of the toxin has been taken up by the haptophile of the cell the toxophore cannot attack the (cell) toxophile. The haptophore thus plays a rôle analogous to that of the amboceptor (immune-body), and the toxophore, or zymotoxic complex, as it is sometimes called, may be compared with the complement. The importance

of this will be apparent when we come to consider in detail the mechanism of antitoxic immunity.

It is thus seen that the lateral-chain hypothesis is based upon specific affinities between the cells and certain organic molecular combinations that may reach them either through the regular process of cell nutrition or accidentally; and that these specific affinities may, depending on the nature of the foreign haptophore, prove harmless, slightly harmful, or destructive to the organism. In the first instance the presence of such haptophores is unsuspected; in the second, it is with difficulty detected; but in the third, such pronounced and uniformly similar effects result that a typical clinical picture is presented. Thus, while most of the specific infectious diseases give rise merely to vague symptoms, a few of them, notably diphtheria and tetanus, afford excellent illustrations of the specific reactions described. Diphtheria poison exerts its effect upon the peripheral nerve-cells with resulting palsy; the poison of tetanus acts upon the nerve-cells in the spinal cord with resulting convulsions. When one comes to view the whole field of organic poisons, one is struck with the frequency with which these specific affinities and consequent specific symptoms occur. We need only mention as typifying these, the paralysis of the respiratory center by serpents' venom and the stimulation of the motor cells of the spinal cord by strychnin.

The lateral chains by which the cellular activities are maintained seem to be susceptible of **regeneration** for the purpose of supplying the needs of the cell, and the regeneration of those lateral chains whose function has been accidentally set aside forms a very important part of Ehrlich's hypothesis. Thus, when an extrinsic and useless haptophore attaches itself to an important receptor, and thereby throws it temporarily or permanently out of function, it becomes necessary that the cell shall form a new receptor of a similar kind, by which the essential molecular group needed for nutrition may be taken up. Should the appropriation of such important receptors by extrinsic and useless haptophores be repeated or persistent, and the need for those molecular groups which are thus prevented from functionating normally become correspondingly great, many receptors of the required kind seem to be formed. In the experimental immunization of animals against poisons such abnormal appropriation of receptors seems to stimulate the production of an excessive number of receptors, in keeping with a general physiologic law, and the number may even become so great as to interfere with cellular activity. When this is the case, the excessive receptors, finding no function to perform, detach themselves from the cell and are

carried away by the tissue-juices. Thus the circulating fluids come to contain groups of molecules having the same combining affinities as the receptors of the cells and permitting the same combinations to take place by their contact with the appropriate haptophores *in vitro* as customarily take place in the body. These constitute the antitoxin (Figs. 4–8).

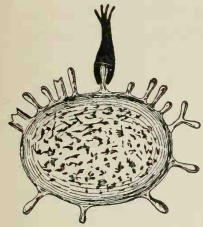

FIG. 4.—FIRST STAGE IN ANTITOXIN FORMATION.—*After Ehrlich* (*Hewlett*).

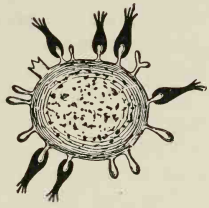

FIG. 5.—SECOND STAGE IN ANTITOXIN FORMATION.—*After Ehrlich* (*Hewlett*).

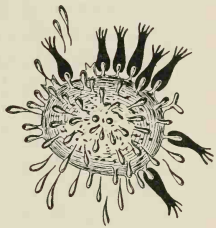

FIG. 6.—THIRD STAGE IN ANTITOXIN FORMATION. Antitoxin beginning to be formed. —*After Ehrlich* (*Hewlett*).

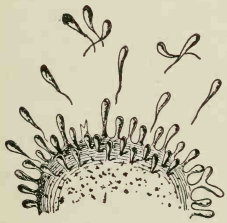

FIG. 7.—FOURTH STAGE IN ANTITOXIN FORMATION. Antitoxin free in the blood.—*After Ehrlich* (*Hewlett*).

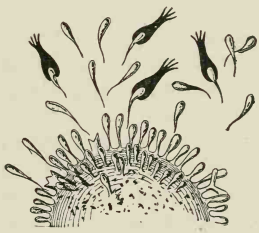

FIG. 8.—NEUTRALIZATION OF TOXIN BY ANTITOXIN IN THE BLOOD.—*After Ehrlich* (*Hewlett*).

Application of the Ehrlich Hypothesis to Immunity.—When we come to apply the lateral-chain hypothesis to the explanation of immunity, we have first to deal with what is known as **natural immunity,** or that insusceptibility to a specific disease which is the peculiar and hereditary condition of the given animal. One of the best illustrations that can be given is that of the rat, which, though smaller than the guinea-pig, is immune against diphtheria toxin when administered in doses ten thousand times as great as will kill a guinea-pig. Chickens are immune against tetanus toxin, many times the fatal dose for guinea-pigs

failing to produce any effect upon them. Tortoises are likewise immune against tetanus, and pigeons against rabies. The immunity in these cases seems to depend in part upon the fact that the cells of these animals do not possess receptors capable of combining with the haptophorous molecular groups of the toxin, whose poison-group cannot, therefore, be brought in contact with their cell protoplasm—thus, in tortoises the toxin remains in the blood for a long time without producing any effect. Again, it may depend upon the inability of the **toxophores** to diffuse themselves through the protoplasm,—toxophilous receptors being absent,—although the appropriate haptophiles are present and the haptophorous combinations are formed. This is probably best typified by the alligator, upon whose cells toxins may make no impression and may occasion no symptoms, though they stimulate the formation of a considerable quantity of antitoxin. *The toxic action and the combining capacity with antitoxin* thus represent *two different functions of the toxin:* and, as we shall have occasion to note hereafter, the former (toxophoric) may become weakened, while the latter (haptophoric) remains constant.

The number of cases in which absolute natural immunity exists is small. Immunity is for the most part relative, and we find that such animals as the hedgehog and mongoose, popularly supposed to enjoy immunity against serpents' venom, are immune against only a certain quantity of venom and rapidly succumb when this is exceeded. Such relative immunity probably depends upon the number of receptors possessed by the cells, which permits the attachment of a great number of toxophorous atom groups before the cellular activities are set aside.

The lateral-chain theory likewise affords the most plausible explanation of the peculiar condition observed in **immunization or acquired immunity.** In this condition the repeated introduction of poisons is followed by an increased tolerance to them. The more frequently the administration takes place and the greater the quantity of poison administered, the more tolerant the animal becomes, provided, of course, great caution be exercised not to destroy life. This peculiarity is explained by the regeneration of receptors. As the animal is obliged to submit to the repeated injections of the poisons, the receptors of its cells are more and more appropriated by the haptophorous elements introduced, provoking in turn a more and more marked regeneration; this increase in number of free combining—*i. e.*, neutralizing—elements bringing about a corresponding increase in the resistance to the poison.

The theory also affords the most satisfactory explanation of the formation of **antitoxin.** The antitoxic quality of the body-juices depends upon the separation of the receptors that have been formed in excess

from the cells whose functions they are beginning to impede. It is the haptophiles that are thus formed in excess and thrown off. By combining with the haptophores of the toxin they prevent the latter from obtaining further access to the cells. The toxophores are thus unable to do harm. Hence toxins in which the poisonous groups have become inactive (*toxones*), while incapable of producing toxic symptoms, can still excite the production of antitoxins effective against toxins of unimpaired power. A study of the accompanying diagrams (Figs. 1–8) will make clear this conception of receptor, haptophore and toxophore, and the various combinations that can be formed. The mode of action of the liberated receptors, as pictured, will give a very clear conception of the toxin-antitoxin reactions.

Hemolysis and Bacteriolysis (Cytolysis).—In considering the evolution of serum therapy allusion has already been made to hemolysis and bacteriolysis, and their bearing on immunity; it now becomes necessary to show through what complicated reactions these peculiar changes are effected.

The original observation of Buchner that the body-juices have the power of killing and dissolving bacteria led to the conclusion that they contain a chemical body, which he called **alexin.*** The results of the investigations of recent years upon hemolysis have shown that this alexin of Buchner may be identical with an active substance found in normal blood and called by some, in deference to Buchner, alexin; termed by others the **complement,** lysin and cytase and named by Ehrlich and his associates in their original work, **addiment.** The complement seems to vary but slightly under normal and abnormal conditions, and the factors governing its variations are by no means understood. As it is a normal product, it seems not to be influenced by experimental manipulation. The general tendency has been to believe that the complement engaged in all forms of hemolysis is one and the same; while another, but a single, form of complement is engaged in all forms of bacteriolysis. Whether that engaged in bacteriolysis is identical with that engaged in hemolysis has been admitted to be at least doubtful. Ehrlich, however, now goes much further and asserts that complements as well as amboceptors are distinct and specific.

The complement acts indirectly, in this respect resembling other enzymes of the body. Thus, thrombase acts upon fibrinogen only in the presence of calcium salts; rennet acts upon caseinogen only in the pres-

* This use of the term alexin is to be avoided, however, as Buchner used the term before the substance causing bacteriolysis had been shown to be complex.

ence of calcium salts; pepsin acts upon proteids only in the presence of hydrochloric acid; and trypsin acts upon the proteids only in the presence of enterokynase. In a like manner the complement—whether universal or specific—acts upon bacteria or blood-corpuscles or other cells, with resulting destructive solution, only in the presence of another substance, variously denominated by different writers on immunity as the *immun Körper*, 'immunizing body' (immune-body), 'desmon,' 'substance sensibilisatrice,' 'fixateur,' and 'amboceptor.'* This immunizing body, or, as it may be best to call it, **amboceptor,** is variable and specific. Various amboceptors are found in the normal blood of many animals, and different kinds of blood vary greatly in the number and kind of amboceptors they normally contain.

Amboceptors are also normal constituents of certain poisons. Thus, Flexner has discovered various amboceptor functions in serpents' venom, such finding the complementary substance through which they act already present in the cells. The best example of this is the cobra lysin, an amboceptor of cobra venom, which destroys blood-corpuscles through the intervention of (complementary) lecithin contained within the corpuscles themselves. It is not known how many such substances are produced in the animal body under pathologic conditions, whether by invading microörganisms or by the body-cells themselves. It is also possible that amboceptors, both beneficial and harmful, may be taken in the form of medicaments, and that certain drugs may thus act through combination with the body-cells or bacterial cells, on the one hand, and with certain chemical constituents of the tissues or tissue-juices on the other hand.

Under artificial stimulation the amboceptors of the body-cells readily increase. Thus when animals are injected repeatedly with foreign blood, amboceptors particularly active against the corresponding blood-cells develop in great excess; and when a particular kind of bacterium is injected, an amboceptor active against that particular bacterium is formed. Similarly amboceptors specifically antagonistic to infective protozoa are probably produced in normal recovery from diseases due to protozoa and in vaccination against small-pox. The amboceptor is thus specific; the complement may be nonspecific or, at least, of multiple specificity—if the term be allowable. The question of the specificity or nonspecificity of the complement is of practical importance, for artificial bacteriolytic immunity depends upon the

* See also page 20 *supra*. Other terms for this substance are: 'ceptor,' 'go-between,' 'linking-body,' 'fixator,' 'copula.'

presence of an appropriate complement. If this be wanting in the animal to be immunized, it cannot be supplied by injecting fresh serum from the same animal that has yielded the immunizing serum (Wassermann). Ehrlich holds that the complements which will satisfy each amboceptor are probably limited in number. Some other animal from another species sometimes furnishes the best complement. When the complement is brought into contact with blood-corpuscles or bacteria in the absence of the appropriate amboceptor, no effect is produced; and, on the other hand, when the appropriate amboceptor is permitted to act upon blood-corpuscles or bacteria in the absence of the complement, no effect is produced; but when a combination of the three takes place, hemolysis or bacteriolysis (cytolysis) results.

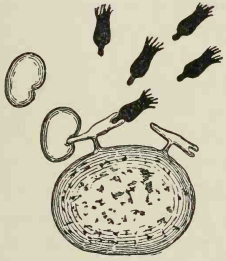

FIG. 9.—AN IMMUNE-BODY OR CONNECTING LINK HAVING TWO AFFINITIES. —*After Ehrlich* (*Hewlett*).

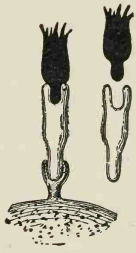

FIG. 10.—DIAGRAM TO SHOW THE UNION BETWEEN COMPLEMENT (BLACK) AND BIOPLASM OF CELL BY MEANS OF THE IMMUNE-BODY (WHITE).—*After Ehrlich* (*Hewlett*).

When a given number of bacteria are to be killed, these must be completely sensitized by '*substance sensibilisatrice*,'—if we take Bordet's view,—or completely saturated with amboceptor (immunizing body),—if we adopt Ehrlich's,—in order that they may become amenable to the action of the complement. Further, there must be a sufficiency of complement present to act fully on the bacteria thus saturated with amboceptor. The blood of an animal treated with the antiserum and dead of an infectious disease ((typhoid) may contain enough immunizing body to protect another individual against a fatal dose of the bacilli (Wassermann). The first animal died because it had not enough complement to enable it to utilize the immunizing body which existed in its blood. An immune serum usually contains an excess of amboceptor, and the therapeutic success depends on the animal's ability to furnish

enough complement additional to that which may exist in the serum to enable it to utilize the amboceptor injected in the latter (Ritchie). Immune serum rapidly loses its complement on being kept (Walker).

Here again a much clearer conception of the amboceptor reactions will be obtained by reference to the diagrams (Figs. 9 and 10) than could be conveyed by any verbal description; and if the conception of appropriate receptors and haptophores is adopted, a glance will show the inability of the complement alone to attach itself to the cell to be dissolved, whereas it is brought at once into contact with the latter in the presence of the amboceptor. A striking simile has been used by E. Fischer to explain the amboceptor reactions. The cell is conceived as a lock, the amboceptor as the key, and the complement as the hand that turns the key. As a rule, only one key or but a few similar ones will fit a given lock, while any hand may turn the key once introduced. So it is with this reaction. The amboceptor is specific; the complement, nonspecific.*

Dose of Amboceptor.—The injection of more than a certain quantity of an amboceptor may be positively injurious, as has been shown by certain experiments performed *in vitro* by Neisser and Wechsberg. In these experiments the complement and the bacteria were kept constant, while the quantity of amboceptor was varied. When the latter fell below or exceeded a certain quantity, no bactericidal action took place. Their explanation is that in a bactericidal mixture containing a sufficiency of complement the effect of adding an excess of amboceptor will vary accordingly as the effect of the linking of amboceptor to complement is to diminish or to increase the affinity of the amboceptor for the bacterial cell. If the effect be diminution, the combined amboceptor and complement will pass the bacteria by, and the latter will thus remain uninjured. Ehrlich found that with certain hemolytic serums there was a greater affinity between the amboceptor and the blood-corpuscle than between the amboceptor and the complement; but in no hemolytic serum has the phenomenon of the preventive effect of excess of amboceptor been observed.

General Antipathetic Properties of Cells.—The facility with which the cells of the body respond to such stimuli as are afforded by the introduction of haptophorous atom groups seems to be so great that an unlimited number of corresponding receptor groups may be formed and discharged

* If, however, Ehrlich's more recent view of the complexity and specificity of complemental substances is established, we shall have to believe that only a hand that knows the "combination" can turn the unlocking mechanism.

into the juices. The stimulation of toxins thus give us what are known as **antitoxins**; of enzymes, **anti-enzymes**; of dissociated tissue-cells and blood-corpuscles, **cytotoxins**; of the cytotoxins, **anticytotoxins**; of amboceptors, **anti-amboceptors** or **anti-immune bodies**; and of complements, **anticomplements** or **anti-addiments.** These were bewildering both in number and characteristics so long as no explanation was afforded by which their formation could be made clear. The lateral-chain hypothesis, however, affords a perfectly satisfactory explanation.

Reconciliation of Immunization Theories

Metchnikoff's hypothesis of immunity has found greatest acceptance among French pathologists and bacteriologists, and is commonly accepted by his disciples at the Pasteur Institute of Paris. In America, where medical thought is distinctly dominated by German influence, the more elaborate and considerably more complicated hypothesis of Ehrlich has found more favor. It can scarcely be said of these two hypotheses that they are altogether discordant, however much they may appear to differ upon superficial examination, and despite the fact that their originators believe them to be opposed and have assumed controversial attitudes. It would seem, on the contrary, that Ehrlich's views might serve as an explanation of the views of Metchnikoff, the former's hypothesis being an accurate means of defining chemically what the latter expressed in different—so to speak, biologic—terms. Thus, in the solution of red blood-corpuscles and other tissue elements by the serum of an immunized animal Metchnikoff remarks that the relation of amboceptor and complement to the cell to be destroyed bears a close resemblance to that of trypsin in the presence of enterokynase, and that the probability is that macrocytase, the enzyme through which he conceives the cells to be dissolved, acts only in the presence of some fixing or sensitizing substance. This seems to be little more than another way of expressing the same general truth.

When narrowed down to the utmost limit, both hypotheses are found to depend upon the action of factors whose nature is not understood, but which must be derived from the cells of the body in response to extrinsic stimulation. In the broad general view appropriate to biologic problems the phenomena are defensive reactions, organized in the course of the evolutionary changes of development and adaptation through which animals, on the one hand, and microörganisms, on the other, have reached their present states and mutual relations. As the editor has elsewhere pointed out,* they illustrate admirably the

* "Disease and Recovery in Their Relation to Therapeutics," Baltimore, 1898.

Spencerian description of life as a continuous process of "adjustment of internal relations to external relations."

GENERAL FACTS REGARDING THE THERAPEUTIC SERUMS

Although all therapeutic serums are similar in that they are derived from experimentally immunized animals, they have little more than this general property in common. Each requires for its successful production—

I. That the essentially active product of the specific microörganism of the disease be utilized in the process of immunization.

II. That a suitable animal be selected for the purpose.

III. That an appropriate method of immunization be carried out.

IV. That the serum of the animal be utilized appropriately.

Any departure from these primary principles must inevitably lead to disappointment.

I. The Active Principle.—For certain of the serums the first problem, that of procuring the essentially active factor of microörganismal activity was simple. The toxins of diphtheria and tetanus and the toxic albumins, ricin, abrin and robin, as well as serpents' venom, with which the pioneers worked, were all easily recognized, readily obtainable and without difficulty demonstrated to be the essential causes of the respective intoxications. But when the attempt was made to apply similar methods in the treatment of diseases other than diphtheria and tetanus, a difficulty was at once encountered from the fact that it is possible to determine in but very few of the specific infections exactly what are the microörganismal products that must be combated. Cultures of the microörganisms of suppuration, of the typhoid bacillus, the anthrax bacillus, the glanders bacillus, the tubercle bacillus and many other similar or dissimilar organisms have been found to be devoid of toxic products, and in the absence of such separable toxins it is doubtful whether a separable antitoxin can result from the experimental immunization of animals.

In the hope that the antibody by which these diseases could be treated might prove of different nature,—if not antitoxic, perhaps anti-enzymic or antimicrobic,—experiments were made upon the same general lines with cultures of the microörganisms of nearly all the specific infectious diseases, but with a greater number of failures than of successes

The work of Vaughan and his associates has shown that the essential

toxic products of many microörganisms are insoluble, and require for their extraction complicated chemical manipulations, an observation which shows how futile is any attempt to secure immunity against such products introduced into the animals while still inclosed in the bacterial cells in which they are elaborated. Crushing the bacteria in the dry state by trituration with finely pulverized quartz and with agate balls, or pulverization of cultures frozen to a quartz-like hardness by liquid air, as practised by MacFadyen and Rowland, and the immunization of animals with the fragments, results in the production of bacteriolytic serums in general resembling those formed in response to repeated injections of the unchanged cultures.

Thus far but two varieties of serums—that is, serums possessed of two different though important properties—have been introduced into therapeutics. As already stated (page 18), the first is the **antitoxic serum;** the second, the **antimicrobic** or **bacteriolytic serum.**

II. Selection of the Animal.—The pioneer experimenters had no knowledge of suitable or unsuitable animals for their experiments. Many of the original investigations were carried out upon rabbits, dogs, goats and other comparatively small animals. Roux introduced the horse for the manufacture of diphtheria antitoxin, chiefly on account of its large size and the great quantity of serum that could readily be obtained from its blood. Subsequent investigators have followed Roux, thinking of the quantity rather than of the quality of the serum that might be obtained; but while antibodies to diphtheria, tetanus and venom are readily manufactured by the cells of the horse, it does not necessarily follow that these will similarly respond to the injection of all sorts of cells, bacterial cultures and toxins.

When we consider the variability among horses, some of which produce enormous quantities and others very small quantities of diphtheria antitoxin after identical experimental treatment, and when we consider, further, the variations in immunity naturally existing among animals of the same kind under the same and different natural and experimental conditions, it must be apparent that the equine species may not be the most suitable for all investigations, and that experiments otherwise based upon sound logical and scientific principles should not be abandoned because such animals fail to furnish a satisfactory serum.

Our knowledge is not yet sufficiently precise to point out what animals are to be used in the different experiments. Future experimenters must determine this point by trial. In general it is to be remembered that painstaking and time-consuming experiments, such as

are under consideration, may be wasted if the animals selected are so small as to furnish insufficient serum for satisfactory therapeutic test.

III. Method of Immunization.—The method of treating the animal must vary. When the specific factor of the disease is toxic, an **antitoxin** is the remedial agent to be hoped for, and can probably be obtained by adhering to the plan originally adopted by Roux, who performed all his immunization experiments with bouillon cultures from which the microörganisms had been removed by filtration through unglazed porcelain.

When the morbific agent produces no soluble toxin, no antitoxin can be looked for as the result of immunization, but the serum will more likely be **antimicrobic** or **bacteriolytic.** To prepare such a serum it will be necessary to introduce the bacteria themselves, the use of filtered cultures being entirely inappropriate and the essential point being the introduction of as many bacteria as possible. Should it be anticipated that the serum will antagonize some enzyme which has been shown to be present, that enzyme should be injected into the experiment animal in order that an **anti-enzyme** may be produced. It is unnecessary to dwell upon this point, as it will be evident, after what has already been explained, that the essential antagonistic characteristics of the serum of the immunized animal will vary according to the peculiar quality of the active agent against which it has been made to defend itself.

The **method of introduction** is of importance. Toxic substances introduced into the blood may act so rapidly as to destroy the animal, or may be eliminated so quickly as to produce no effect upon it; whereas the same cultures, introduced into a subcutaneous cellular tissue through which they would be slowly absorbed and brought in small quantities to the cells, might lead to entirely different and highly gratifying results. When it is found by experiment that the introduction of microörganisms beneath the skin, or of toxic substances into the cellular tissue, is followed by local lesions of such magnitude as to be in themselves dangerous, the opposite plan may be adopted, and the irritating substance injected into the circulation, where it at once meets with such dilution as to destroy its irritating effects. Thus, in immunization experiments, each case is more or less a law unto itself, and must be carefully considered and investigated along independent lines.

IV. Administration.—Many of the disappointments of serum therapy have been the result of exalted anticipations and insufficient information. The highly gratifying results following the application of serum therapy to the treatment of diphtheria and the close relationship that appears to exist between the diphtheria and tetanus antitoxins aroused

the hope that equal success would accrue from the use of the tetanus antitoxin in the treatment of lockjaw. Experience has shown, however, that the course of tetanus is much less certainly modified by the administration of the antiserum. This is, however, in the natural order of things; for the action of tetanus toxin upon the nerve-cells is so prompt and energetic that by the time symptoms have developed it is difficult for antitoxin to break loose the combinations of haptophiles and haptophores, toxophiles and toxophores, already formed. Were it not that we have in diphtheria a peripheral lesion which arrests the physician's attention before the toxin has had time to act upon the nervous system, the results following the treatment of diphtheria with antitoxin would unquestionably be different. If the lesion in diphtheria were inaccessible; if the first indication of infection were diphtheric palsy and the administration of antitoxin had thus to be deferred until palsy had occurred, an exact parallelism between diphtheria and tetanus would be found and the limitations surrounding the antitoxic treatment of diphtheria would be as great as those in tetanus.

It is hardly necessary to point out that the mode of action of the antimicrobic serums is so entirely different from that of the antitoxic serums that a much less energetic action is to be expected of them. These serums dissolve bacteria in the test-tube; if in the test-tube, why not in the circulating blood? But when the therapeutic utilization of such serums is attempted, it is found that they are exceedingly irregular in action and variable in effect. We are now in a position to understand this variability. The introduction of bacteria into the organism of the experiment animals leads to the formation of an **immune-body** (amboceptor) only. This immune-body can effect the destruction of bacteria only in the presence of the complement, and the varying effects observed to follow the therapeutic administration of antimicrobic serum must depend upon the varying quantities of complementary substance in the blood of the patient and in the serums introduced. From test-tube experiments the inference seems justifiable that if some satisfactory method of increasing the complement* in the blood of the experiment animals could be devised, a practical utilization of the immune-body in their serum might be feasible; but so long as no increase of the complement is possible, no practical result can accrue from the administration of the immune-body. Indeed, it seems true that in nearly all those

* The usefulness of certain physiologic methods and certain drugs in one or another infection may some day find its explanation in their power to increase the production of immune-bodies or of complement, or to take the place of one or the other.

cases in which it seems desirable to attempt to influence the course of an infectious disease favorably by introducing a serum rich in immune-body, the blood of the patient already contains more than enough of that same body, but lacks sufficient complement to enable it to destroy the invading microörganisms. A few of the antibodies are distinctly antitoxic. Certain others are distinctly antimicrobic or bacteriolytic; but the literature contains many elaborate investigations dealing with serums whose nature is neither one nor the other, whose activity is extremely uncertain and whose mode of action is unknown.

In considering what effects will follow the administration of any serum the investigator should have before him an accurate description of its mode of preparation in order that he may carefully think out through what means and under what conditions it is operative, and what results can be expected. It too often happens that the preparation has been the result of hurried and thoughtless experimentation and that the serum has no justifiable use. From this consideration of the subject, as well as from an analysis of the clinical facts thus far published, we are obliged to conclude that the present outlook of serum therapy is narrowly limited. As so often happens, that which was most evident, most active, and most useful was discovered first—in this instance the antidiphtheric serum, which can truthfully be said to be useful for the treatment of all cases of diphtheria and to have reduced the mortality of that disease by more than one-half.

Antitetanic serum is shown by the statistical study of large numbers of cases to have produced a distinct diminution in the death-rate from tetanus, although isolated observations have led many to believe its curative value extremely doubtful. Its prophylactic value cannot be doubted. Guinea-pigs can be protected from many times the fatal infection or intoxication by the preliminary administration of the serum, but experiment conclusively shows that the longer the time elapsing between the infection or intoxication and the administration of the serum, the less certain becomes the action of the serum.

Antivenene (Calmette), when administered prior to invenomation, acts as a prophylactic against cobra poison, and in the treatment of a small number of cases has apparently saved life in cases of cobra bites. Its sphere of usefulness is distinctly limited, as it exerts scarcely any effect upon viper venoms. Noguchi has recently announced the successful preparation of an antagonist to rattlesnake venom, but as yet there has been no opportunity for clinical observation therewith.

Other serums have had a fugacious clinical or literary recommendation, but it cannot be said that their usefulness has been demonstrated.

CHAPTER II

SPECIAL SERUM THERAPEUTICS

Diphtheria and the Antidiphtheric Serum. Tetanus and the Antitetanic Serum. Snake-bite and Antivenene. Suppuration and the Antistreptococcic Serum. Pneumonia and the Antipneumococcic Serum. Typhoid Fever and the Antityphoid Serum. Tuberculosis, Tuberculin and Antitubercle Serum. Plague and the Antiplague Serum. Dysentery and the Antidysenteric Serum. Hay-fever. Leukemia and other Blood-diseases. Leprosy.

DIPHTHERIA AND THE ANTIDIPHTHERIC SERUM

The poisonous products of the diphtheria bacillus were first separated by filtration, and studied by Roux and Yersin; later they were carefully studied by Brieger and Fraenkel. The most painstaking attempts to isolate the toxic substance were probably made by Brieger and Boer. The toxic substance is freely soluble in water, so that it readily escapes from the bodies of the bacteria and diffuses through the bouillon in which they are cultivated. It was at first supposed to be an albuminous substance, and was looked upon as a toxalbumin. It is, however, doubtful whether the poison is albuminous in nature, for which reason it is at the present time commonly described as a toxin rather than as a toxalbumin.

All diphtheria bacilli are supposed to produce toxin and its formation is held to be the most satisfactory mode of differentiating the true diphtheria bacillus from the pseudodiphtheria or Hoffmann's bacillus. The diphtheria bacilli, however, vary very greatly in their toxin-producing power, and for the manufacture of strong toxin, such as is required for the immunization of animals, a particular bacillus of exceptional activity must usually be selected. The toxin production is also influenced by such external conditions as the composition and reaction of the nutrient substratum, the temperature at which the bacillus is cultivated and the length of time during which it grows. It is also profoundly influenced by other products generated by this same bacillus.

The most accurate information regarding toxin production has been afforded by the investigations of Theobald Smith. He found that the bacillus grown in beef bouillon containing two per cent. of peptone and

five-tenths per cent. of dextrose first attacks the dextrose, causing its decomposition with the liberation of acids, and that during the period of this activity the bouillon remains free from toxic properties. When the dextrose becomes exhausted, the bacillus seems to attack the proteid substance in the bouillon; alkalis are formed and soon neutralize the primary acidity, their continued formation causing the reaction to become increasingly alkaline It is only during the period of alkalinity that toxin is formed.

Preparation

The Toxin.—The usual laboratory method of preparing diphtheria toxin as a preliminary to the production of antitoxic serum is to make use of this knowledge of the metabolism of the diphtheria bacillus, and grow massive cultures in appropriate fluid media, which are subsequently freed from the bacteria by filtration and employed for the immunization of the experiment animals. A first-class toxic bouillon is so poisonous that from one to three thousandths of a cubic centimeter will kill an adult guinea-pig and from one-half to one cubic centimeter may kill a susceptible horse. This toxin, when protected from bacterial contamination and reasonably well defended against the effects of light, heat and oxidation, will keep for a number of months, during which time its virulence becomes gradually attenuated. This change depends upon the change of the toxin into toxoids, which, while retaining their power to combine chemically with the antitoxin, are devoid of death-dealing power toward the experiment animals. (See page 28.) Nearly all toxins and numerous other active bodies undergo similar subtle chemical changes, knowledge of which is important in all investigations upon the problems of immunity. Its most important bearing is upon the estimation of the value of diphtheria antitoxin, and forms the foundation of the Ehrlich system of antitoxic units, as will be explained later on.

Immunization of the Animals.—Behring's original experiments were performed upon goats, but Roux greatly facilitated the commercial preparation of antitoxin by recommending the horse. When the serum of the immunized animal is to be used upon human beings, it is necessary to make a careful selection of the experiment animal, which must be free from communicable disease and in the best general health possible. The selected animals are given increasing doses of toxic bouillon of known strength, at intervals varying from a few days to a week, the quantity of the toxin being increased as rapidly as is possible without producing obvious injury to the horse. Some horses can be immunized in this way in a few months; others may require twice as long. There is no limit

to the administration of the toxin except that necessitated by consideration of the comfort and health of the animal. Thus, it is possible to introduce without danger quantities as great as a liter; but beyond this it is scarcely advisable to go. The horse thus receives increasing injections of toxin, followed by an increased production of antitoxin, until the maximum quantity of toxin to be injected is reached. Each injection produces a definite reaction. In animals under immunization an injection of toxin is always followed by a decline in the quantity of antitoxin in the blood, which, when graphically represented by a curve, shows a descent continuing for about three days, and then a very marked ascent, the greatest quantity of antitoxin being formed about the tenth day, after which it slowly declines and then remains for a long time unchanged. The final outcome varies much in different individuals, some animals producing large quantities of antitoxin, others scarcely any. The cause of these variations has not yet been determined.

As we have already seen (page 29), it is the combination of haptophorous with haptophilic elements that gives rise to the regeneration of receptors, the toxophores and toxophiles playing no part in it. The experiment animals should, therefore, receive injections of carefully chosen culture products in which are contained a maximum of haptophorous and a minimum of toxophorous substance. By these means the safety of the experiment animal is greatly enhanced.

The process as a whole can readily be explained on the basis of the lateral-chain theory of immunity, the formation of antitoxin probably depending upon the liberation of excessively regenerated receptors following each toxic injection. The toxic injections are made in the subcutaneous tissue wherever it is loose—usually about the neck and shoulders of the horse. When thrown into the blood, the toxin seems to be eliminated too rapidly to effect the necessary impression upon the cells.

Preparing the Serum.—When a test of the blood shows that it contains sufficient antitoxin to be practically utilizable, the trocar is introduced into the jugular vein and as much blood as can conveniently be taken without injury to the horse is drawn into sterile containers, permitted to coagulate and the clear serum pipetted off.

No satisfactory method of extracting the antitoxin from the serum containing it has been devised. It can be precipitated with various agents, but the resulting precipitates contain the various globulins as well as the antitoxin, and are not freely soluble. They can also be precipitated as double salts of the heavy metals, but when so precipitated cannot be separated again from the metals.

The antitoxins are comparatively **stable bodies,** and the serum con-

taining them retains its power sometimes for one or two years with very little appreciable change. They are not affected to any considerable degree by putrefaction of the serum, by light, oxidation or ordinary variations of temperature, so that when the serum containing the antitoxin is dispensed in sterile receptacles, it retains its properties for a long time. It is customary to add an antiseptic to the serum in order to prevent accidental contamination, and for this purpose trikresol, carbolic acid and formaldehyd are used.

Determining the Strength.—*The Antitoxin Unit.*—The method of testing the activity of the antitoxin is somewhat important, as different methods lead to slightly different results; and it is of the utmost importance to know that the serum selected for therapeutic use has the activity desired. The strength of the serum is expressed in so-called **immunizing units,**—a term devised by Behring,—determined by estimating the amount of toxin neutralized by a given quantity. In the method originally formulated, which was used for many years in Germany and in this country, the smallest fatal dose of toxin for a 300-gram guinea-pig was carefully ascertained. Then to each of a series of guinea-pigs ten times this dose of toxin, mixed with varying quantities of antitoxin, were administered. The least quantity of antitoxin that would save the life of a guinea-pig thus intoxicated was ten units. According to this system, a unit was ten times the quantity of antitoxin that would protect a 300-gram guinea-pig against ten times the smallest fatal dose of toxic bouillon. That the quantity of antitoxin capable of neutralizing the ten fatal doses should be one-tenth of a unit was a matter arbitrarily fixed by Behring in devising his standard, apparently to make a unit the quantity necessary to neutralize 100 doses.

This method of testing was considered satisfactory until Ehrlich began to investigate the nature of diphtheria toxin and showed it to be extremely labile. Even while the culture is growing in the incubator Ehrlich finds that the toxin already formed begins to degenerate into less poisonous or nonpoisonous products, which he describes as **toxoids**—molecular combinations in which toxophorous groups are assumed to be deficient or wanting. All toxic bouillon therefore contains toxin and toxoids, and both of these bodies are capable of combining with antitoxin. Certain of the toxoids have a more marked affinity for antitoxin than has toxin itself. Therefore Ehrlich was led to believe, and his demonstration of the facts is very convincing, that unless allowance is made in some way for the varying proportion of toxoids in the toxic bouillon, they must invariably cause confusion in the test. If the bouillon contains few toxoids, the antitoxin unites with the toxin and neutralizes it. If, on the other hand, the bouil-

lon contains many toxoids, the antitoxin added may combine first with the toxoids and leave the toxin free. Thus a given quantity of antitoxin added to bouillon whose fatality for guinea-pigs is approximately the same may neutralize much or little of the toxin contained in any one specimen of bouillon according to the opportunities it may have for combining with toxoids. In consequence of this defect in the original mode of testing Ehrlich devised a new system, based upon the antitoxin-neutralizing value of the toxic bouillon instead of upon the fatality of the bouillon for guinea-pigs. From every standpoint this system is so superior to the original method that it has met with almost universal adoption.

The first desideratum in Ehrlich's system is a standardized and invariable antitoxin, by which the combining power of any toxin can be standardized. To secure this a serum whose strength was calculated as accurately as possible, according to the old plan, was chosen. It was evaporated to dryness and finely pulverized; then distributed in small glass tubes having a lateral tubulature with a small bulb containing phosphoric anhydrid. By means of a mercury pump the air contained in each tube was removed, and the tubes were hermetically sealed. Ehrlich found that when antitoxin in a dry state was thus protected from oxidation it was very slow to change, and solutions of it could be used as a standard probably for years. From time to time tubes of this powder were opened and appropriate solutions made, so that one cubic centimeter contained exactly one unit, which unit became the standard of comparison in testing other serums. When fresh serums are to be tested, any toxic bouillon selected for the purpose of making the test may first be standardized as to its antitoxin-neutralizing value by determining the least quantity which, when mixed with one unit of the standard antitoxin, will kill a guinea-pig of 250 grams weight in four days. This dose of toxin Ehrlich denominates **L+**, because it is a quantity which has exactly neutralized all the antitoxin and contains one lethal dose in addition. In toxic bouillon without toxoids this should equal 100 lethal doses, but, as a matter of fact, on account of the presence of toxoids, it rarely equals more than 80.

After the antitoxin-neutralizing dose or unit of toxin has been accurately determined by these means, this quantity is administered to each of a number of guinea-pigs, and varying quantities of the antitoxin to be tested are added until it can be determined what is the least quantity that will save the life of the guinea-pig. That quantity is one unit of antitoxin.

The unit has been arbitrarily chosen and merely affords a con-

venient measure of strength. Thus, when it is known how many of these units an antitoxin contains, we know, as a result of past experience with antitoxin, what quantity of it must be administered either for therapeutic or for prophylactic purposes.

So far as is known, the diphtheria antitoxin is specific in its action upon the diphtheria poison and is without neutralizing effect upon any other poisonous substance.

Administration

Antidiphtheric serum must always be administered by subcutaneous injection. It is not absorbed through the mucous membranes, and when taken into the stomach, is digested. Experiments made to protect guinea-pigs by the ingestion of the serum have either failed or been too irregular to be conclusive.

Prophylactic Dose.—The serum is administered either for prophylaxis or for therapeusis. For children the administration of 500 units, for adults from 500 to 1000 units, affords sufficient protection against the disease, this protection lasting for from one to three months.

Therapeutic Dose.—For treatment, the peculiarities of the individual case must carefully be considered. An initial dose of 2000 units is probably as small as should be employed; in severe cases it is well to begin with 3000 or 4000 units. It seems to be essential to produce a marked impression upon the case at once by neutralizing all the toxin present with the first injection, and if possible, cure should be effected by this first injection. As there is no proof that the serum when pure and free from contamination produces untoward effects, very large quantities may be administered if necessary, and an unlimited administration of the remedy, such as has been carried out in the Boston City Hospital, has without doubt resulted in the saving of lives. The rule has been to administer large doses and to repeat them every four hours until a distinct beneficial result is obtained. If no definite improvement follows the first injection, a second should be given in from four to six hours; if this also fails, a third should be given after the same interval, and so on.

The theoretic objection that has been urged against certain antiserums, that they lead to the formation of bodies by which they themselves are neutralized, does not militate against the diphtheria antitoxin, as it probably always finds enough toxin in the blood of the patient.

Few **precautions** are necessary in the use of antidiphtheric serum. The syringe with which the injection is made, or the needle through which the serum is introduced, in case one of the ingenious packages now upon the market is used, should be thoroughly sterilized and the skin carefully

cleansed and disinfected. Three practical points must be considered in estimating the value of the remedy:

1. *The time at which it is prescribed.* Statistics show that with the passage of each day the beneficial effect of the antitoxin diminishes, because of combinations formed between the toxin and the nerve-cells.

2. *The quantity of the remedy that is prescribed.* Many cases have no doubt succumbed because the remedy has been used too cautiously.

3. *The necessity for accurate diagnosis.* It is only in diphtheria, not in all forms of pseudomembranous angina, that antidiphtheric serum can be expected to effect a cure.

It has been said that diphtheric palsy is more frequent after the administration of antitoxin, but there seems to be a very reasonable explanation for this. Under the administration of antitoxin many lives are saved which under other modes of treatment must inevitably have been lost. Therefore, under the administration of antitoxin very many bad cases of diphtheria recover. It is well known that diphtheric palsy is most apt to follow bad cases of the disease; through antitoxin, therefore, very many cases are preserved from death to recover with subsequent palsy. We find, however, upon careful examination that it is only in cases in which too little antitoxin is used, or in which it is not early enough prescribed, that palsy occurs.

Effects of the Injection.—Immediately after the injection of a sufficient dose of the antidiphtheric serum gradual improvement can be noticed. The patient soon becomes brighter, the pulse is stronger, the prostration is lessened, and a change can be observed upon inspecting the throat. The mucous membrane contiguous to the diphtheric membrane becomes hyperemic and in a few hours the patches of membrane begin to separate. If the dose administered has been sufficient to cure the disease, the membrane either rapidly exfoliates, completely detaching in the course of a few hours, or it quickly melts away. It is not uncommon for complete casts of the pharyngeal wall or of the lining of the larynx to be expectorated in cases of complete exfoliation; though when the membrane melts away, shreds of it are frequently swallowed until it all disappears. After the complete disappearance of the membrane the angina rapidly subsides, but living virulent diphtheria bacilli may remain in the throat for a long time—sometimes for several months—and during the period of their persistence the patient may be a source of danger to others.

The attempts that have been made to use diphtheria antitoxin against **pneumonia** and other nondiphtheric infections deserve mention only historically.

TETANUS AND THE ANTITETANIC SERUM

Nature of Tetanus Toxin.—The tetanus bacillus elaborates a most powerful toxin. So powerful is it that it ranks among the most deadly substances known, and its activity in minute doses has given rise to the hypothesis that it is a ferment which, when introduced into the body, transforms the body-juices into poisons. It is probably not simple in constitution. The toxic bouillon, indeed, contains a number of active substances that have been isolated by different observers. Brieger, in his first investigations, extracted four poisonous substances from tetanus cultures, of which all were poisonous for mice, with more or less marked spasmodic effects. Ehrlich found the tetanus bacillus producing two toxic substances which he called respectively **tetanospasmin** and **tetanolysin.** It is to the first of these that the tetanus spasms are due; the second expends its action upon the red blood-corpuscles.

Wassermann and Takaki have shown that the poisons combine with the **nervous tissues.** This was, of course, supposed to be the case from clinical observations made years previously, but the actual demonstration of it was made when these observers crushed the tissue of the central nervous system and suspended its cellular elements in salt solution. On bringing the tetanus toxin into contact with this solution a combination resulting in the complete neutralization of its toxic properties was observed to take place. This affinity for the central nervous system is so marked, and the combination between the two so stable, that once the haptophore of the toxin attaches itself to the receptor of the cell, and the toxophorous atom groups produce a sufficient amount of disturbance to provoke symptoms, it is well-nigh impossible, through the activity of the antitetanic serum, to undo the mischief. Recent observations tend to show, moreover, that the toxin is diffused by way of the nerve-tissues, rather than by the blood or lymph channels, thus explaining many of the clinical phenomena of the disease and at the same time reinforcing the lesson of promptitude in preventive treatment.

Tetanus toxin resembles the poison of diphtheria in being freely soluble, ordinary bouillon cultures being suitable for its preparation. Cultures of this kind, filtered through porcelain, possess all the toxic properties of the bacilli and can be utilized for the immunization of animals which are to furnish the antitetanic serum. As the immunization of the experiment animals is carried on according to the same general principles described in speaking of the antidiphtheric serum, no further description will be necessary. The animals are immunized, their blood collected, and the serum treated in the same way.

Administration.—Three methods for the therapeutic administration of antitetanic serum have been suggested—**subcutaneous injection, subdural injection** and the application of the dry, powdered serum to the infected wound.

A comparison of the results obtained by subcutaneous injection and subdural injection does not indicate that the latter has any great advantage over the former. Nor has it been shown that an injection of the substance into the brain can be looked upon with favor.

Considering what is known of the action of tetanus toxin and the limited action of the antibody we are not surprised to learn that its practical application has been disappointing in many cases.

Mortality.—In the studies of Packard and Willson of the cases reported during 1900–1902, inclusive, they obtained the following figures: "Of 1216 cases collected (including 290 cases gathered by Moschcowitz and other similar series reported by different observers) treated with antitoxin by the various methods we find that 702 recovered and 514 died, giving a mortality of 42.2 per cent. Very few cases have been reported during this time in which the antitoxin treatment was neglected, and we have been able to collect only 67 in the literature at our command. Of these, 18 recovered and 49 died, giving a mortality of 73.1 per cent. This discrepancy in the percentage mortality, however, may appear greater than it actually should. The latter series is so small, and the tendency to report unfavorable cases so slight, that we have hardly adequate material for a proper comparison with a series of such dimensions as that included under the antitoxin treatment; we are, therefore, driven to a comparison of older records for information as to the percentage mortality of tetanus to its treatment by antitoxic sera. Moschcowitz states that Richter collected 717 cases with a mortality of 88 per cent.; that Behring gives a mortality of 80 to 90 per cent.; Gower, one of 90 per cent.; Raynaud, of 90.5 per cent.; and that Dean has obtained from a study of all the cases in the London hospitals in sixteen years a mortality of 80 per cent. Probably the latter figure is much nearer the average death-rate than the higher figures quoted. Lambert notes 1222 cases occurring in war surroundings (mortality, 88.6 per cent.) and 280 cases in time of peace (mortality, 76 per cent.). His own experience includes 35 cases, with a mortality of 83 per cent. The general mortality of tetanus in the Civil War (505 cases) was 89.3 per cent. Lambert has also published a series of 262 cases treated with antitoxin, with 151 recoveries and 111 deaths—a mortality of 42.36 per cent. (in the acute cases of 72 per cent. and in the subacute and chronic cases of 16 per cent.). Nearly all observers who have reckoned from a con-

siderable number of cases agree with him in his figures, so that we shall not occupy time and space by adducing other names and statistics.

"From a study of as many authorities as it was found possible to consult we find it the general consensus of opinion that the mortality of tetanus prior to the introduction of antitoxic serum was between 70 and 90 per cent. (usually approaching the lower figure); of the acute form, between 80 and 90 per cent.; and of the chronic form, 25 to 40 per cent. Lambert states the former mortality of the disease as 88 per cent., and of the chronic form as 40 per cent. In any event, statistics seem to denote a reduction in the general mortality from the conservative figure of 80 per cent. to one between 40 and 50 per cent.; of acute tetanus from 90 per cent. to 70 to 80 per cent., and of chronic tetanus from 40 per cent. to about 20 per cent.

"Moschcowitz cites the mortality in cases treated with antitoxin by various observers as follows:

	Cases.	Mortality.		Cases.	Mortality.
Marsden	38	34.2 per cent.	Wellner	94	45.0 per cent.
Hewlett	42	36.0 "	Weischer	98	41.8 "
Engelmann	54	29.6 "	Holsti	171	43.2 "

"It would seem, therefore, that we have in tetanus antitoxin not a specific, because it fails too often to have merited such a name, but a valuable remedy in the treatment of the disease, and one that ought not be neglected until a better is supplied."

As cases of tetanus are in reality quite rare, and the demand for the antitetanic serum therefore small, many manufacturers market their serum in the form of a **dry powder,** which represents the original serum dried in vacuo. This powder has the advantage of keeping much longer than the serum itself, but has the disadvantage of being soluble with difficulty.

Dosage.—We have no knowledge as to how much tetanus antitoxin must be administered to effect a cure. It is not at all unlikely that many of the failures have taken place because an insufficient amount of the remedy has been prescribed. Yet this is not the chief trouble with the tetanus antitoxin. Under most accurate experimental conditions the unlimited administration of the remedy often fails to produce a favorable impression upon an animal fatally intoxicated. The only directions that can be given those who desire to employ the serum in the hope of doing good are to use it so soon as the first symptoms of the disease appear, and to administer it frequently in very large doses.

Unit.—Behring and Knorr have introduced an arbitrary unit by

which the antitoxic strength of the antitetanic serum can be expressed. It is difficult to define this unit in plain terms, but it seems to represent the least quantity of the serum that will protect a 250-gram guinea-pig against 1,000,000 fatal doses of fresh toxin. If the test be made upon white mice, one unit must protect against 300,000 minimum fatal doses of toxin. The difficulty of understanding and of accurately determining this unit has made most manufacturers follow the French suggestion of expressing the strength of the serum in relation to the number of grams of guinea-pig protected. Thus, it is commonly stated on the label: "The strength of this serum is 1 : 1,000,000, 1 : 10,000,000, etc.," indicating that one gram of the serum is capable of protecting 1,000,000 or 10,000,000 grams of guinea-pig, as the case may be, against fatal intoxication.

Prophylactic Value of Antitetanic Serum.—Although the antitetanic serum has shown itself unable to combat all cases of tetanus, even though they may be treated very early and with what must be considered a sufficient quantity of the serum, it finds a most important application in prophylactic medicine, and this phase of its employment is by no means receiving the commendation and application that it merits. In a paper written in conjunction with E. M. Ranck I have called attention to an experience in this particular sphere that deserves great consideration. In one of the large antitoxin factories in which large numbers of horses were being manipulated, the death-rate from tetanus at one time reached ten per cent., and it became a serious problem how to continue to operate against such terrific odds. It finally occurred to me that the systematic immunization of all the horses might be a means of overcoming the difficulty, and when this was done, by the regular employment of antitetanic serum at trimonthly intervals, the death-rate immediately fell from ten per cent. to less than one per cent. These observations were made upon more than 800 horses. The practice has since become general in antitoxin and vaccine establishments and should, indeed, be made obligatory by law.

Surgical dispensaries and clinics constantly receive cases of lacerated, incised and punctured wounds polluted with soil, in which the nature of the injury and the attendant circumstances lead at once to the suspicion that tetanus may develop, and unfortunately in a very large number of these cases it does develop. If, however, each of these patients at the same time that his wound is opened and treated were to receive a prophylactic injection of the antitetanic serum, there is little doubt that many lives would be saved.

Local Application.—In a recent communication before the Academy

of Science at Paris, Calmette called attention to the fact that the antitetanic serum is readily absorbed from the surface of wounds. Hence it is not necessary to give subcutaneous injections in early cases, but an excellent prophylactic method of treatment is to dust the **antitetanic powder** freely upon the surface of the wound. I have been able fully to confirm this suggestion of Calmette and in recent experimental work have by this method perfectly protected intentionally infected animals against the fatal effects of the tetanus organism.

SNAKE-BITE AND ANTIVENENE

Antivenene.—Phisalix and Bertrand observed that the blood serum of guinea-pigs immunized against serpents' venom acted as a vaccine against venom. This observation was soon followed by the more elaborate investigations of Calmette, who showed that when a solution of cobra venom was heated to 70° C. for an hour and then filtered,—by which the locally irritating properties of the venom were completely destroyed and the nervous poisons permitted to remain intact,—a progressive introduction of the filtrate into animals was followed by the appearance in their serum of a neutralizing substance which he called **antivenene.** Finding this antivenene sufficiently active to protect against many times the fatal dose of cobra venom thus modified by heat, Calmette recommended its employment in the treatment of snake-bite in general and endeavored to show that in all serpents' venom the important poison to be combated was one capable of withstanding the application of heat, and whose injurious action depends upon its specific effect upon the respiratory centers. In a number of cases of snake-bite, chiefly bites of cobras, the serum was put to practical test with most satisfactory results, and the hope was expressed that in this serum an ideal treatment for snake-bite would be found.

C. J. Martin, however, has shown that Calmette is incorrect in his assumption that the venoms of different snakes are so nearly identical in constitution, and has brought forward ample evidence to show that antivenene is inactive against the venoms of the Australian snakes. My own investigations have shown that antivenene is practically useless in combating the venoms of the American snakes; which, with the exception of the elaps, a small snake of the Southern States very rarely known to bite, belong to the Viperidæ and have venoms whose locally destructive activity greatly outweighs their influence upon the central nervous system, so that these bites are extremely painful and destructive, but rarely cause death. When the venoms of the American snakes—

rattlesnakes, copperhead and moccasin—are heated to 70° F. as suggested by Calmette, a heavy precipitate forms, which, when removed by filtration, takes from the solution of venom nearly all the locally irritating substance, and leaves in the solution a small quantity of a nerve-poison similar to that found in the cobra venom. Against this element of the venom antivenene affords thorough protection; but against the irritating substance contained in the venom it affords no protection, and my own endeavors to produce an antibody active upon this irritating substance met with signal failure. Noguchi has since met with better success and has produced a serum perfectly efficient in animals if used within three hours after the injection of venom and in quantities rapidly increasing with the time elapsed after the invenomation.

Different observers have made contradictory reports regarding the action of venom upon the blood, some finding it coagulated very promptly, others finding coagulation unduly delayed, and some that the corpuscles are dissolved. The solution of the corpuscles depends upon a principle which has been described by Stevens and Myers as cobra lysin. When dilute solutions of the venom are brought into contact with a dilution of defibrinated blood, the venom brings about a rapid solution of the corpuscles. If, however, a strong solution of the venom is brought into contact with a similar dilution of the defibrinated blood, solution of the corpuscles does not take place. Flexner has shown that the solution of the corpuscles depends upon an amboceptor function of the cobra lysin. Ehrlich found that the solution depends upon the presence of the lecithin in the corpuscles, for which cobra lysin seems to have a great affinity, so that diluted venom and lecithin combine in the corpuscles and effect their destruction. If stronger solutions are used, the lecithin is withdrawn from the corpuscles, forming a compound apart from it, and the solvent effect is inhibited. Anticobra lysin is easily prepared, and, indeed, exists in Calmette's serum.

The hemorrhagic extravasations characterizing the bites of many snakes have been shown by Flexner and Noguchi to depend upon an endotheliolysin for which they suggest the name hemorrhagin. It is thus evident that many different destructive elements are present in venoms, and therefore that protection against the action of venoms cannot be afforded by antitoxic serums, such as antivenene, alone.

Calmette's recommendations for the **treatment of snake-bite** are as follows:

1. If possible, place an elastic ligature tightly above the seat of the bite, so as to prevent absorption of venom by the blood-vessels.

2. Inject immediately into the seat of inoculation and in several

places about the bite and at no great distance from it, from 20 to 30 c.c. of a fresh one per cent. solution of chlorid of gold or calcium.

3. Remove the ligature and wash the part with a large quantity of a sodium hypochlorite or calcium chlorid solution.

4. As soon as possible administer to the patient, by subcutaneous injection, 20,000 units of antivenene.

Attention is called to the fact that antivenene is made an adjunct to the treatment of snake-bite and that it is of the utmost importance to prevent the absorption of the poison as much as possible, and to effect chemical neutralization by the hypodermatic injection of a fresh solution of calcium chlorid before absorption takes place.

Unit.—Calmette recommends the following method for **standardizing** and determining the value of antivenene. A standard solution of venom is prepared, the unit of this solution to be based upon the quantity of venom necessary to kill a rabbit of two kilograms in twenty minutes by intravenous injection in the marginal vein of the ear. The indicated quantity corresponds on an average to two milligrams of cobra venom and to four milligrams of rattlesnake venom weighed dry. An antivenomous serum, to be sufficiently active for therapeutic use, must be protective in the minimum dose of two cubic centimeters when injected into the ear vein fifteen minutes before the injection of the venom.

The **efficiency of antivenene** is thus found to be greatest against the venoms of the East Indian snakes, and experience as well as experiment has shown that upon the venom of the cobra it exercises a decided neutralizing effect. Fortunately, snake-bite is uncommon in America and opportunities for its practical investigation have thus been few. For the theoretic reasons mentioned serum therapy cannot be looked upon as more than an adjunct to the treatment of snake-bites, and upon the venoms of the Australian serpent Martin has shown that it has scarcely any influence. The serum is **administered** by **subcutaneous injection,** in doses of 10 c.c., repeated as frequently as necessary.

SUPPURATION AND THE ANTISTREPTOCOCCIC SERUM

There is no specific microörganism of suppuration, which is the result of the chemotactic activities possessed by different products of numerous bacteria. Thus, in slightly varying conditions we may find in purulent exudates staphylococci, streptococci, gonococci, pneumococci, meningococci, typhoid bacilli, colon bacilli and various other organisms. Remembering the specific activity of all antibodies, it is scarcely to be expected that an antiphlogistic serum potent against all these different

factors could be prepared, although a serum protective against each seems possible.

Unfortunately, we know nothing about the nature of the streptococcus. The filtered cultures of the most virulent organisms are usually quite inert, so that the different poisonous substances contained in these microörganisms must be insoluble and intracellular, and the antibodies produced by immunization against cultures must belong to the antimicrobic and bacteriolytic rather than to the antitoxic serums. Upon theoretic grounds the possible explanations of the inactivity of antistreptococcic serums are quite numerous. In the first place, we are not yet certain that the various streptococci morphologically and culturally similar are identical, so that it is not impossible that the streptococcus against which the experiment animal may be immunized differs from that against which its immune serum is to be utilized, when, of course, no result can be expected. In the second place, it is a very common observation that streptococci virulent for one animal are harmless for others. Assuming that the lateral-chain hypothesis of immunity is correct, and that increase of virulence depends upon the immunization of the microörganism against the defensive cellular products of its host,—as has been suggested by Walker and emphasized by Welch,—we can conceive that the virulence of streptococci experimentally manipulated in the laboratory may become great in those particular animals against whose defensive mechanism it is immunized by repeated passage at a time when it is in reality undergoing no increase in virulence for other animals; and possibly this increase may be wanting as to the very animals subjected to the immunization process for the production of the antiserum. Whether or not this be true, and even should the microorganism become virulent both against those animals through whom it is passed in the laboratory in order that its virulence may be increased and against those into which it is injected for the production of the antiserum, it may still remain nonvirulent for human beings; and hence the antibodies formed in the experiment animal may prove inactive against microörganisms possessing virulence for human beings when the attempt is made to employ the serum therapeutically. Finally, the serum being antimicrobic or bactericidal, its action is indirect and probably effects the dissolution of the bacteria only through the coöperation of amboceptor (immune-body) and complement. As with similar serums in general, the excess of amboceptor is useless in the absence of the necessary complement. Should the therapeutic serum contain no increase of complement and the serum of the patient be deficient in this necessary factor, failure must result.

In a recent report made to the American Gynecological Association, 101 cases (of puerperal septicemia) were cited in which bacteriologic examination had demonstrated the presence of streptococci. These gave a mortality under the serum treatment of 32.6 per cent. (33 deaths); in 251 cases in which no bacteriologic examination was made there was a mortality under serum treatment of 15.85 per cent. (40 deaths), giving a total of 352 cases and 73 deaths—a mortality of 20.74 per cent. Upon the basis of these findings the committee advised that further experimentation with the serum was not justified.

Packard and Willson found records of 117 cases treated during the previous two years with antistreptococcic serum, and in 114 of these there was either a marked temporary improvement or a prompt recovery. The cases included puerperal septicemia, erysipelas (mild and malignant), tuberculosis with pyogenic infection, general pyemia, and local streptococcous infections. They also cite a few cases of pernicious anemia and of simple anemia that seemed decidedly improved by injections of the serum.

The first serum of this kind was the antistreptococcic serum of Marmorek, which is best known and has been most thoroughly tried. Antistaphylococcic serum, investigated by Viquerat, has been less favorably received.

Marmorek's Serum.—This serum was first prepared by Marmorek by the immunization of ponies to increasing quantities of living cultures of streptococci made virulent by passage through rabbits and intermediate cultivation upon a special medium. The immunization of the ponies extended over a period of a year or more, and a considerable interval was permitted to elapse between the last injection and the withdrawal of the serum, in order that the streptococci might disappear from the blood of the experiment animals. Subsequent manipulations of the animals and of the serum were not peculiar.

Administration.—Antistreptococcic serum cannot be expected to afford the least benefit in cases of suppuration depending upon microorganisms other than the streptococcus. Therefore, in estimating the success or failure attending the use of the remedy, a bacteriologic examination must always be made. There is no method of calculating accurately the value of the serum, and its strength cannot be expressed in **units** or by any other means by which the clinician can measure the power or determine the **dosage.** It is customary to administer from 10 to 20 c.c. by subcutaneous injection and to repeat this dose frequently. Our knowledge of the subject is empirical only, and the products of different laboratories all vary in strength and must in consequence yield varying results if active at all.

At this point it may be well to call attention to one danger that attends the use of all forms of antimicrobic serums. They all contain both complementary and immune-bodies. It has been shown by Ehrlich that when either of these factors is repeatedly injected into an animal, antibodies are produced by which their activity is destroyed; that is to say, the general law of reaction applies and anti-immune bodies and anticomplementary bodies are formed. In the event of the serum not being able to effect good through the proper combination of amboceptor and complement, it is conceivable that repeated injections might do harm through the formation of these antibodies.

Indications.—As particularly appropriate for remediation through antistreptococcic serum Marmorek points out **erysipelas, streptococcous suppuration, pyemia** and **scarlatina.** To these may be added certain cases of **puerperal infection, angina** and possibly **small-pox,** as Councilman has recently shown that there is scarcely any infectious disease in which the invasion of the body by streptococci is so marked as in small-pox.

Lilienthal, after stating that he has never known a patient to recover when streptococci had been clearly demonstrated in the blood-stream, summarizes the indications for the employment of the serum in surgical cases as follows:

The bacteria are to be sought for in the discharges from the wound and in the urine, and cultures should be made from the discharges and from the blood.

If the urinary sediment contains streptococci,—determined by microscopic examination,—the prognosis is very bad, and serum treatment should be begun at once, together with other methods of general and local antisepsis. If the patient's condition is very serious and streptococci are found in the smear from the wound, the serum should be used even if the bacteria are not present in the urine; but if the general condition is not alarming and no streptococci are found in the urinary sediment, it is better to await the result of the blood-culture test.

Treatment by streptococcic serum is most strongly indicated in the presence of **systemic infection by living streptococci,** but the prognosis is always grave. The efficacy of the remedy has not been proved.

PNEUMONIA AND THE ANTIPNEUMOCOCCIC SERUM

This serum has resulted from the experimental investigations of de Rienzi, Washbourn and Pane. It is prepared by the immunization of horses and other good-sized animals against progressively increasing

doses of virulent pneumococci. It is an antimicrobic or bactericidal serum, subject to all the theoretic arguments already brought forward in discussing the antistreptococcic serum. In general it may be said to have been disappointing in the results obtained by clinical demonstration. Like the antistreptococcic serum, no means have been devised for accurately determining its value or calculating the necessary dosage, and we have in reality scarcely any accurate information concerning it. It is customarily administered by subcutaneous injection in doses of from 10 to 20 c.c., frequently repeated.

Rabbit serum has been used by Lara Bozzolo and de Rienzi in twenty-five cases in all, with only one death. Wiesbecker asserts that he has obtained striking improvement with **human convalescent serum,** as originally suggested by Klemperer, though Hughes and Carter were disappointed in their results with it. Much is claimed for **Pane's turkey serum,** which has been tested extensively by Italian investigators. It is said to lower the temperature, improve the pulse and assist resolution; the actual number of deaths is said to have been lower than with any other mode of treatment. Bordoni believes that the serum acts on the general condition more than on the local process. Fanoni of New York reports six cases of pneumonia treated with Pane's serum with one death. The disease was not abridged, and the temperature came down by lysis. Fanoni also noted the good effect on the general condition. De Rienzi reports thirty-two cases with three deaths.

According to Lambert's experience with twelve cases, three of which ended fatally, the serum causes a slight reduction of temperature and an improvement in the pulse. It did not cause a crisis in any case and did not cut short the pneumococcic process, nor did it prevent complications. The serum had no effect on the leukocytes except in one case, when it caused an increase of 10,000. His conclusion is that it does not shorten the duration of the disease and is therefore not valuable. It may save life in some cases by preventing a general pneumococcus septicemia.

TYPHOID FEVER AND THE ANTITYPHOID SERUM

Numerous experimenters, among whom are Fraenkel, Pfeiffer, Widal, Levy, Wright, Bokenham and Chantemesse, have written upon antityphoid serums, and from time to time efforts have been made to apply in the treatment of typhoid fever certain serums thought to have value from experimental and theoretic data. These serums have all passed into oblivion with the exception of those of Bokenham and Chantemesse, of which we still hear occasional echoes.

Serum of Chantemesse.—One of the chief difficulties to be overcome is the insoluble and purely intracellular nature of the poisonous products of the typhoid bacillus, which made it impossible to immunize animals except by the use of cultures of the bacteria. These cultures, whether living or dead, were found to be so irritating and their injection was so universally followed by local induration and necrosis as to make it scarcely possible to immunize large animals. Chantemesse, however, seems to have obtained a toxic product by a special method of cultivation, in which the bacilli are grown under anaërobic conditions upon a filtrate of an emulsion of splenic tissue digested with pepsin. The toxic power of this culture disappeared when it was exposed to the air. Horses were found to be very susceptible to the poison, and little immunity was developed during the first year of treatment. Later, however, they acquired immunity and their serum became bactericidal, and was found to possess both prophylactic and therapeutic value. One hundred cases of typhoid fever were treated with this serum. All those treated before the tenth day recovered, and of the remainder, all recovered but six. In two of the fatal cases serum treatment was first substituted on the twenty-first day of the disease; one patient died of pneumonia, and one of a preëxisting extensive gangrenous sloughing. All the 100 cases would be clinically described as bad cases, and all were in hospitals except ten. The serum injection was said to be followed in a few hours by a slight febrile reaction and a decided improvement at the end of about thirty-six hours. The temperature falls, there is marked diuresis, and if the temperature subsequently reascended, a second injection of the serum always caused a rapid decline. The **dose** of the serum is said to be from 10 to 12 c.c. for vigorous adults, repeated if necessary. In early cases of disease a smaller dose, 6 to 8 c.c., may be given in the beginning. Concerning this remedy we have no information except from Chantemesse.

TUBERCULOSIS, TUBERCULIN AND ANTITUBERCLE SERUM

Koch's Tuberculin.—In 1890 Koch announced some observations upon the toxic products of the tubercle bacillus, which culminated in the preparation of a bacterioproteid to which he gave the name **tuberculin.** As originally prepared, it consisted of a 50 per cent. glycerin extract of cultures of the tubercle bacillus, though later the preparation was modified.

Preparation.—At present massive cultures of the bacillus are grown upon glycerin bouillon in flasks, in which a thin layer of the culture

medium exposes an extensive surface to the air, so that upon a really small amount of culture medium a great number of bacilli can grow. At the end of some weeks the thick, wrinkled pellicle of bacilli that appears on the surface becomes saturated with moisture and sinks to the bottom, and from the time the pellicle sinks, very few bacilli can be made to grow by a replantation upon the surface. If, however, the flasks be agitated so as to wet the pellicle artificially and cause it to sink to the bottom, another pellicle will form upon the surface. When the growth of the microörganisms has ceased, the contents of the flask are shaken up and poured into a large porcelain evaporating dish and concentrated to one-tenth the volume by boiling over a water-bath. The resulting brownish, somewhat heavy fluid is then filtered through diatomaceous earth or a Pasteur-Chamberland filter, and the resulting filtrate is **crude tuberculin.** From it Koch subsequently prepared a refined or **purified tuberculin** by adding one and one-half volumes of absolute alcohol, stirring thoroughly and standing aside for twenty-four hours. At the end of this time a flocculent deposit settles at the bottom of the vessel. The supernatant fluid is carefully decanted and an equal volume of 60 per cent. alcohol poured into a vessel for the purpose of washing the precipitate, which is again permitted to settle, the fluid decanted, and the washing thus repeated several times, after which it is finally washed in absolute alcohol and dried in a vacuum.

Uses of Tuberculin.—Tuberculin is almost harmless for healthy animals, but is extremely poisonous for tuberculous animals, its injection into them being followed either by violent febrile reaction or by death, according to the extent of the disease and the size of the dose administered. Koch hoped that tuberculin, because of a peculiar reaction that it brought about in the tissues of tuberculous guinea-pigs, and because guinea-pigs repeatedly injected with it lived longer than tuberculous guinea-pigs usually do, might prove efficacious as a therapeutic agent, and with his recommendation behind it the remedy was received with universal acclamation and immediately put to the test in all countries. The results were most disappointing, and at the present time tuberculin is rarely employed except as a means of diagnosticating tuberculosis in cattle. It was found by experience that its effect was injurious rather than beneficial; or, when it was administered in minute doses, so that no injurious action resulted, there was no effect. The only purpose for which it is employed in human medicine at the present time is to establish the diagnosis of the disease in obscure cases.

Koch's Tuberculin R.—In 1897 Koch was heard from a second time on the subject of tuberculin. This communication had to do with a

new tuberculin, or tuberculin R, an entirely different preparation, supposed to contain the essential toxic products of the tubercle bacillus. It was **prepared** by mechanical fragmentation of living virulent tubercle bacilli, a mode of treatment which Koch seems to have borrowed from Klebs. The organisms were pulverized in agate mortars while living and virulent, but perfectly dry, very small quantities being triturated at a time. After the bacilli had been reduced to fragments they were removed from the mortar, placed in distilled water, washed and collected by centrifugation as a muddy sediment at the bottom of an opalescent clear fluid. In order to separate the essential poisons of the bacteria as perfectly as possible from the irritating tuberculin, the fragments were again perfectly dried, again triturated, again collected in fresh, distilled water and recentrifugated a second time. After the second centrifugation microscopic examination showed that the bacillary fragments had been resolved into a uniform mass. Koch found the tuberculin R to possess decided **immunizing powers,** and suggested utilizing it according to the plan suggested by Pasteur in the treatment of rabies to bring about immunity during the slow development of the chronic disease.

The disappointment that had been experienced with tuberculin militated against tuberculin R, which was received with great caution and used with hesitation. The new tuberculin proved to be as disappointing as tuberculin itself. Some of the best experimenters, as, for example, Baumgarten and Waltz, failed to confirm Koch's assertion that tuberculin R immunized guinea-pigs against tuberculosis. Trudeau and Baldwin found live and virulent tubercle bacilli in the fluid, so that it came to be looked upon with suspicion, and at the present time it is probably very rarely employed.

The **composition of the tubercle bacillus** seems to be extremely complex. Klebs found the bacillus to contain two **fatty bodies** of different chemical reactions. De Schweinitz extracted an **acid resembling teraconic acid ;** Ruppel believes that three different fatty substances are present in tubercle bacilli, making up from 8 to 26 per cent. by weight. He also found a protamin which he called **tuberculos-amin.** From these he later isolated an acid which he called **tuberculinic acid.** Behring found that this acid contained a histon-like body, whose removal left chemically pure tuberculinic acid. One gram of this acid, when introduced beneath the skin, destroyed 600 grams of guinea-pig, and when introduced into the brain, 90,000 grams of guinea-pig. When injected into tuberculous guinea-pigs it was much more fatal, one gram destroying 60,000 grams upon subcutaneous injection, and 40,000,000 grams when

injected into the brain. Levene isolated a **combined nucleinic acid** and a **glycogen-like substance** that resists Fehling's solution when heated with a mineral acid. These elaborate chemical studies of the bacillus have not yet shown us what are its essential toxic products, nor discovered for us which of them must be employed in successfully immunizing animals or producing antibodies.

The Antitubercle Serums.—Numerous attempts have been made to prepare efficient antitubercle serums. Names familiar to those who have read the literature upon the subject are those of Tizzoni, Centanni, Bernheim, Paquin, Maragliano, Babes, Proca, Mafucci, di Vestra, de Schweinitz, Fisch and Patterson. Many different plans for immunizing animals intended to produce the antibodies have been tried. Some use tuberculin in the hope of finding an antituberculin which might counteract the injurious effects of tuberculin produced in the body. De Schweinitz and others introduced nonvirulent bacilli in the hope of producing a bactericidal or antimicrobic serum. Fisch assumed the tuberculin R to be the essential toxic substance of the bacillus and injected horses with it, and Patterson utilized the avian tubercle bacillus. The published reports rarely carry much conviction with them. The number of cases upon which the serum was tried by each investigator is usually small, and those familiar with tuberculosis and the therapeutic problems associated with its treatment are well aware that any new mode of treatment is apt to impress the patients favorably and bring about a decided temporary improvement.

Maragliano publishes his results for the period 1900–1901, under treatment with his own antitoxin, and obtains the following figures: In the year closing with June, 1901, 130 out-patients were treated and 36 clinically cured (including 17 with fever and destructive processes and 3 with cavity formation). Improvement was noted in 58; in 31 the condition remained stationary; and in 5 the disease progressed. He states, however, that it is impossible to cure without reënforcing the strength of the organism.

The time has not yet come when the state of serum therapy in tuberculosis can be regarded as hopeful.*

* In a more recent communication (1904) Maragliano asserts that he has been able to produce an antituberculous serum perfectly protective to guinea-pigs and other animals, and from which he entertains high hopes of successful protective inoculation in man. It is too soon to pass final judgment on these reports.

PLAGUE AND THE ANTIPLAGUE SERUM

The plague bacillus discovered by Yersin and Kitasato apparently forms no soluble extracellular toxin or produces such toxin in small amounts and only when highly virulent. No chemical method has yet been devised for extracting a satisfactory toxic substance from the bodies of the bacilli for use in the immunization of experiment animals in the preparation of antiplague serums. The antiserums thus far prepared, therefore, belong to the **antimicrobic** rather than to the antitoxic serums. It must be remembered, however, that in the absence of accurate information concerning the chemistry of such microörganisms as the streptococcus, staphylococcus, gonococcus, typhoid bacillus and plague bacillus, and total absence of information as to just what reactions take place when cultures of these microörganisms are introduced into experiment animals in progressively increasing quantities, this separation of the resulting products of immunity into antitoxic and antimicrobic serums is altogether artificial, and it may be that serums act upon any toxin that is present or upon the microörganisms, or upon both.

Yersin's Serum.—The antiplague serums first suggested by Yersin are prepared by injecting horses intravenously with increasing quantities of cultures of live, virulent bacilli. The serums of such horses can be shown experimentally to afford the laboratory animals complete immunity against virulent cultures of the plague bacillus and in cultures containing toxin annul the effects of the poisonous substances present.

These serums have been used in human medicine with considerable success, but in order to be efficient, enormous quantities of the serum—sometimes amounting to several hundred cubic centimeters each day—must be administered, and to obtain the best effects it is recommended that the injection be made into a vein.

Serum of Lustig and Galeotti.—Lustig and Galeotti prepared a serum by injecting horses with a bacterioproteid extracted from massive cultures of the plague bacillus, and assert that its effect is more marked than that of the serum of Yersin. The serum is used for **prophylaxis** as well as for treatment. Proskouriakoff reports concerning the last severe epidemic at Bombay as follows:

"Between August, 1899, and March, 1900, 52 persons were treated with the serum, with 35 deaths (67.3 per cent.) and 17 recoveries. Of 162 cases not treated with serum, 125 died (77.16 per cent.) and 37 recovered. During March, April and May, 1901, 104 persons were treated with the serum, with 81 deaths (77.82 per cent.) and 21 recoveries. Of the foregoing, the cases of a septicemic type gave a mortality of 96.6

per cent., and those of a nonsepticemic type one of 56.6 per cent. The septicemic cases treated without serum gave a mortality of 98.1 per cent., and the nonseptic cases one of 61.5 per cent." This shows that in Bombay no very considerable beneficial effect resulted from the use of the serum.

Value of Antiplague Serums.—Mason treated two series of cases—100 with Yersin's serum and 100 without. The mortality in the first group was 59 per cent., in the second, 83 per cent. These results are, however, subject to the fluctuations observed in epidemics, as the first series was treated during a declining epidemic and the second series at the acme of another epidemic.

Simond treated 300 cases at Karad and elsewhere with Yersin's serum, the mortality being 58 per cent., while the mortality in the same hospitals in cases treated without the serum was 75 per cent. Choksey reports the following series of cases: "(1) Of 257 serum cases, the mortality was 22.7 per cent. less than in 752 other hospital cases, including the untreated and the moribund cases which were not included in the serum count; (2) 403 cases treated with serum gave a diminution in the death-rate of 18.7 per cent. as compared with 1190 patients treated during the same period without serum; (3) 968 patients treated with serum showed a diminution in the mortality of 11.5 per cent. as against alternate cases treated without serum."

The minor accidents from antiplague serum made at Rio are, according to Crug, disturbances, cutaneous manifestations, adenitis and pain in the joints and muscles. These were not severe enough to interfere with the individual's daily work and vanished in a few days. Among the more serious accidents are mentioned high temperature, intense pain, erythema, purpura, erysipelas, arthralgia, pulmonary phenomena, delirium, prostration and adenitis accompanied by symptoms which suggested the plague. Out of a total of 123 patients injected with the serum 58, or 47.17 per cent., exhibited accidents, but in only 7 were the accidents of a serious character. At Frionl the proportion of accidents observed was 44.7 per cent., and at Glasgow, 47.3 per cent. The immunizing effect of a prophylactic injection appears to last from eight to fifteen days. The dose employed is about ten centimeters. The serum prepared at the local institute is heated for an hour to 135° F. (57° C.), which destroys its toxic properties.

While in the main the results accruing from the use of the antiplague serum appear favorable, upon comparing a large number of reports from different sources one is obliged to admit that the diminution in the death-rate is rarely striking. The Russian Commission appointed to

investigate the antiplague serum reports it to be an "absolutely indifferent substance, with no influence either for good or evil on the course of acute plague," and the British Commission appointed for the same purpose finds that Yersin's serum contains "therapeutically useful substances in greater or smaller quantity."

DYSENTERY AND THE ANTIDYSENTERIC SERUM

In 1899 Celli, Fioca and Scala reported the discovery in the stools of dysentery of a peculiar form of *Bacterium coli* which they called *Bacillus coli dysenteriæ* (variety dysenteriæ). This microörganism may or may not be identical with that described the year previous by Shiga, and called by him *Bacillus dysenteriæ*, and looked upon as the specific cause of the epidemic dysentery of Japan. The same bacillus was found in epidemic dysentery in the Philippine Islands by Flexner, and later in sporadic dysentery in the United States by Vedder and Duval. Still later Duval and Bassett found it in the stools of infants suffering from summer diarrhea, especially when such diarrhea was epidemic; and it would seem probable that many cases of what were formerly known as diarrhea, enterocolitis, cholera infantum and the like are really cases of infection by this microörganism.

Its toxic products have not yet been discovered. It is found, however, that the immunization of horses against cultures of the virulent organism is followed by the elaboration of an antiserum capable of protecting small animals against the effects of the organism, and apparently able to produce a favorable impression upon patients suffering from dysentery and from summer diarrhea.

The use of the antiserum was tested by Shiga in Japan, who pronounced upon it favorably, and extensive investigations of the value of the serum in the summer diarrhea of infants are now in progress under the auspices of the New York Board of Health, the Rockefeller Institute and others.

HAY-FEVER

Hay-fever, rose cold, or Bostock's catarrh is an irritative disturbance caused by a poison contained in the pollen of certain grasses. The **specific substance** is probably identical in all the varieties of grass that have been found capable of producing the disease; it is contained, according to Dunbar, in the pollen of rye, barley, wheat, rice, maize and other grasses to the number of eighteen, which he tested; while the pollen from linden trees, roses and many other plants is quite innocuous. The vegetable

toxin attacks the mucous membrane of the nose and the conjunctivæ of predisposed individuals. The rectal mucous membrane of some persons is also susceptible.

The specific substance which Dunbar isolated from the pollen is insoluble in ether and alcohol, but more or less soluble in water and physiologic salt solution, hence also in the lacrimal and nasal secretions, the saliva and blood serum. It is not pure starch, but is described as an **albuminoid body.** In order to demonstrate the etiology of hay-fever Dunbar made a series of experiments in December and January on susceptible and on immune individuals, using a solution of the pollen of maize by hypodermatic injection. Subcutaneous injection of a solution of this substance induced in predisposed individuals the typical symptoms of hay-fever, and, in addition, marked cyanosis, dyspnea showing itself by inspiratory stridor, urticaria and general tumefaction of mucous membranes; the temperature remained normal. The duration of the attack varied from a few hours to several days, depending on the size of the dose. The same doses administered in the same way to persons not predisposed to the disease were absolutely without effect.

Serum.—For the preparation of his **prophylactic** and **curative** serum Dunbar selected Indian corn, the pollen of which, after being reduced to powder, was dissolved in water and centrifugated. With this serum another series of experiments was undertaken in January, 1903, on eight hay-fever patients and eleven control individuals free from any tendency to hay-fever. After a dose of the toxin had been administered as in the first series of experiments, a few drops of the serum were instilled into the conjunctiva, with the result in each instance of preventing the attack, or, when the instillation was delayed until symptoms had made their appearance, cutting the attack short. Experiments were also made with a serum obtained from immunized animals.

Dunbar concludes that *it is possible to neutralize the pollen toxin with serum* in vitro *absolutely or practically so;* and as the dose of poison used in the experiments is probably much greater than the quantity to which patients are usually exposed, he believes that the outlook for serum therapy in hay-fever is hopeful. Clinical experience with Dunbar's antitoxin seems to show that, when repeated sufficiently often, its local application is palliative in many cases, but that it fails in at least an equal number and is not, strictly speaking, curative in any. It is probable, however, that antiserums appropriate for the various exciting pollens or other substances may be found useful in cases selected according to exciting agent. The subject deserves further experiment and clinical trial. Dunbar's serum is marketed under the name

of pollantin. A drop is instilled into each conjunctival sac and three or four drops into the nasal chambers of each side on rising in the morning. This induces a temporary insensitiveness to the usual causes of irritation. The application is to be repeated when necessary. Self-immunization according to the method of Curtis, by internal administration of an extract of an appropriate exciting agent (rag-weed, golden-rod, clover-top, etc.) several weeks in advance of the expected period of suffering, is also helpful in many instances.

LEUKEMIA

Leukolytic antileukemic serum, prepared by Lucatello and Malon through inoculation of rabbits and sheep with the sedimented leukocytes from the blood of leukemic patients, appeared to have some leukotoxic effect *in vitro*, but the clinical results in the three cases in which it was tried were insignificant. Some shrinking of the spleen was detected. It may be remarked in passing that not enough experimental work has been done upon the serum therapeutics of the blood diseases.

LEPROSY

Rost of Calcutta has prepared from lepra bacilli cultivated in a special medium a substance called **leprolin,** which, injected into lepers, causes violent reaction, the temperature rising to 104° F. and the patches becoming red, hot and swollen. Repeated injections are followed in most cases by marked improvement in the patient's condition; in some cases there is almost complete subsidence of the disease. The report states that of thirty-five patients thus treated, two have apparently recovered, while the others seem to be upon the road to recovery. Much more extended observation with this substance will be necessary, however, before its true value can be determined.

ORGANOTHERAPY

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CHAPTER I

EXTRACTS OF THYROID, THYMUS, PITUITARY AND SUPRARENAL GLANDS

Introductory Remarks. Definition of an Internal Secretion. Scope of Organotherapy. THYROID GLAND: *Parathyroids; Iodothyrin; Rodagen; Physiology and Toxicology; Graves's Disease; Therapeutics, Myxedema and Cretinism; Goiter; Adiposis Dolorosa; Struma thyreopriva; Obesity; Skin Diseases; Insanity; Dysmenorrhea; Eclampsia; Carcinoma; Nephritis; Akromegaly; Hemophilia.* THYMUS GLAND: *Rickets, Graves's Disease, Vasomotor Ataxia, Infantile Atrophy, Marasmus, Hemophilia, Scurvy.* PITUITARY GLAND: *Gigantism and Akromegaly, Pulmonary Hypertrophic Osteoarthropathy.* SUPRARENAL GLAND: *In Ophthalmologic and Rhinologic Work, in Genito-urinary Diseases, Uterine Hemorrhage, Gastric and Intestinal Hemorrhage, Heart Failure, Shock, Vasomotor Debility, Internal Hemorrhage, Asthma, Addison's Disease, Pruritus; Epinephrin, Suprarenin, Suprarenalin, Adrenalin, Adrenalin Chlorid.*

Organotherapy (from ὄργανον an organ, and θεραπεία, care, nursing—verb θεραπεύω, to do good, to treat) is the treatment of disease by means of preparations made from the internal organs of animal bodies.

This treatment rests on a scientific and rational basis, the result of physiologic investigations of the various internal secretions elaborated by the ductless and some of the other glands of the body. An **internal secretion** is one that is taken up directly by the lymph vessels of an organ or gland and is not poured out through a gland-duct. These secretions are necessary to health, and if they are much increased or greatly diminished, disease or disturbance of the system is the consequence. Other preparations of animal tissues and juices are likewise employed in therapeutics.

The **secreting structures** now chiefly utilized in the treatment of disease are the thyroid, thymus, pituitary, suprarenal, mammary and parotid glands, the pancreas, the spleen, the testicles and the ovaries. To complete our study of the subject, the therapeutic uses of nuclein, lecithin, glycerophosphates, gastric juice, secretin and muscle serum are likewise described, and reference is made to extracts of the prostate gland, mucin, brain and kidney extracts (**opulins**) to some of the most used organic serums and to the therapeutic procedure known as transfusion. The uses of what may be termed the external secretions—pepsin, pancreatin, trypsin, oxgall (inspissated bile), etc.—are not considered here.

S. Solis Cohen has pointed out that the therapeutic uses of animal tissues and secretions fall into three principal categories:

1. **Homologous** or **direct physiologic organotherapy,** in which actual or relative deficiencies in the functions of certain organs of the patient are remedied by the administration of functional substances derived from similar organs of the lower animals. This is best illustrated by the use of digestive ferments in indigestion and of the thyroid preparations in myxedema. A further subdivision could be based on the use of *external* or *internal* secretions. The digestive ferments may stand as a type of the former; the thyroid preparations represent the latter.

2. **Physiologic organotherapy of the indirect type,** in which the apparent function in the human body of a certain organic product leads to the administration of the like substance from animals for the production of a similar effect; and this, even when disease or deficiency of the given organ or secretion is not to be demonstrated or may not be suspected. The use of adrenal substance locally or internally to produce vasoconstriction is the most conspicuous example of this class.

3. **Heterologous organotherapy,** in which the pharmacologic properties of substances of animal origin are used for the production of effects having no necessary reference to the physiologic uses or pathologic capabilities of the living structure in the human body. As strychnin or arsenic affects the animal metabolism and produces certain toxic or therapeutic results, so do substances of animal origin: the use of thyroid-gland preparations in diseases of the skin is an instance in point, and it may be that such uses will be found for all animal extracts.

THYROID GLAND

The thyroid is a ductless gland with colloid material as its internal secretion. Adjacent to this gland are small portions of tissue resem-

bling it in structure and called parathyroids. There may also be nodules of thyroid tissue, irregularly placed in the region of the thyroid gland, which are known as **accessory thyroids.** Hence, in order to deprive an animal of all thyroid secretion, not only the thyroid gland but all accessory thyroids must be removed, and even then some of the subsequent symptoms may be due to the concomitant removal of the parathyroids.

Chemical Composition.—The **colloid material** of the thyroid is a mixture of two albuminous bodies representing the active secretion of this gland. There is a small amount of phosphorus found in the gland and a nucleo-albumin occurs in the cells of the acini. In 1895 Baumann discovered **iodin,** formerly supposed to be a substance foreign to the body, in this colloid secretion. Later he elaborated a dry proteid substance containing iodin, to which he gave the name of **thyroiodin** or **iodothyrin,** and which appears in some cases, but not in all, to be practically equivalent in therapeutic value to thyroid extract.

The thyroid gland is probably the only organ of the body that normally contains iodin. The adult gland holds in combination about four milligrams of this element, the amount varying at different ages and in different localities as well as in different conditions of the gland itself. The largest amount of iodin is found between the ages of twenty-five and fifty-five. Colloid goiters contain a considerable amount of iodin, while the ordinary cystic goiter shows no increase of this element. As the result of elaborate researches, Gautier and Bertrand believe **arsenic** to be a normal constituent of the thyroid gland; Gautier places the amount at 0.75 milligram in 100 grams of thyroid tissue. The average weight of a normal thyroid gland in the adult man is about 30 grams (one ounce).

Physiology

In 1859 Schiff first described the effects of thyroidectomy, but his observations were lost sight of until 1884, when he reported that after complete thyroidectomy dogs developed tremors and convulsions and died within two weeks. He also showed that these symptoms do not occur when a considerable portion of the gland is left behind; nor do they occur if, before thyroidectomy is done, a piece of thyroid gland be grafted into the skin or into the peritoneum. These experiments have been confirmed by Halsted, who also made the observation that removal or injury of a portion of the thyroid will cause the rest of the gland to hypertrophy and thus produce the normal amount of secretion.

A large part of our knowledge of the value to the economy of thyroid

secretion has been acquired through the study of myxedema and cretinism—*i. e.*, from a study of the pathology of the gland.

Myxedema was first described, though not named, by Gull in 1873, but the connection between this condition and the thyroid gland was not recognized until 1878. Horsley showed that thyroidectomized monkeys developed myxedema, and other observers have shown the same to be true of other animals with but few exceptions. When in young children the thyroid is absent or undeveloped, the condition of **cretinism,** with its stunted growth, impaired brain development and myxedematous skin, occurs.

In 1882 Reverdin described the symptoms of myxedema which develop in man after complete removal of the thyroid gland, and Kocher noted that these symptoms were most marked in young subjects and hardly appeared at all in old age. According to Schäfer, they consist of apathy, diminution of cutaneous sensibility, dryness of the skin, falling out of the hair, an increase of the mucin in the connective tissue, especially of the skin, lowering of the temperature, unsteadiness of the gait, tremors, clonic spasms, and finally convulsions. All these symptoms can be prevented in animals and man by feeding with thyroid extract. It has also been demonstrated that animals show the results of thyroidectomy much later when fed on milk than when on a meat diet; Breisacher states that thirty per cent. of thyroidectomized animals will remain alive for a long time on a milk diet, although they soon die when fed on raw beef. Possibly, in this percentage of the animals operated on there were supernumerary thyroids which, however, did not produce sufficient secretion to protect the system against the toxins of raw beef. The observation suggests, as Ewald has pointed out, that in all conditions of diminished thyroid secretion, notably myxedema, the diet should consist of milk and vegetables.

Physiologic and Toxic Effects

Thyroid substance is broken up in the stomach and forms various combinations, but the gastric juice does not impair its activity.

Metabolism.—Dogs and men fed on thyroid extract or iodothyrin lose weight, have an *increased flow of urine* and an increased excretion of nitrogen, sodium chlorid and phosphorus (P_2O_5). The diuresis is probably due to the increased amount of urea excreted, though all of the increased nitrogen loss is not in the form of urea.

Chittenden suggests that the cause of retarded calcification and bone growth in cretins is due to the inability of the thyroid gland to provide the phosphoric acid (P_2O_5) in proper form for the needs of the body.

Heart and Vessels.—As Cyon found vasodilator fibers in the thyroid nerves, he inferred that one of the functions of the thyroid is to *dilate the blood-vessels* and prevent hyperemia of the brain. Intravenous injections of thyroid decoction *lower the blood-pressure* without directly affecting the heart. Animals deprived of their thyroids react much more rapidly to external change of temperature than normal animals; in other words, their *heat-regulating mechanism is impaired.* It is quite possible that vasomotor regulation of heat loss and heat retention is aided by the secretions of the thyroid and suprarenal glands, these secretions being reflexly affected by external temperature. The excessive administration of thyroid preparations will cause feebleness of the heart, lowered blood-pressure, tachycardia, flushing of the surface, excessive sweating and even syncope. A case has been reported of sudden death from heart failure, in other words, a complete vasomotor paralysis, due to excessive thyroid feeding.

Internal Chemistry.—It is a generally accepted theory, supported by the evidence of constantly accumulating facts, that thyroid secretion renders innocuous certain toxic substances circulating in the blood. The urine of animals deprived of their thyroids is more toxic than the urine of normal animals. It has also been shown recently that injections of certain toxic substances into the thyroid gland seem to be innocuous, while the same substances injected elsewhere produce inflammation. Excessive thyroid secretion, whether from hyperactivity of the gland or from overfeeding with the extract, causes irritation of the central nervous system; Moebius has found serum from thyroidectomized sheep—presumably containing substances normally neutralized by thyroid secretion, and therefore theoretically capable of neutralizing an excess of the latter—of marked value in reducing the nervous irritation of Graves's disease.* The thyroid gland also appears to have some influence in restricting the development of connective tissue, as in cases of diminished thyroid secretion this tissue is increased in various parts of the body.

These facts show the potency of thyroid secretion and emphasize the care with which thyroid preparations should be administered.

Effects of Pathologic Changes in Thyroid Secretion

After ligation of the thyroid vessels degenerations take place in the brain and spinal cord; but what relation diminished or disturbed thyroid

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*In one case under the editor's observation, however, thyroid enlargement and cardiac palpitation were markedly increased by a preparation of milk from thyroidectomized goats.

secretion may have to nerve degenerations in man has not yet been discovered. In **cretinism** the thyroid gland is absent, undeveloped or cystic, and when present contains but a minimum of colloid material. In **myxedema** the thyroid gland may or may not be diminished in size, but the glandular parenchyma is replaced by connective tissue; there is but a small amount of colloid material and the iodin is greatly diminished or absent.

It is generally conceded that, whatever may be the original cause or whatever part the sympathetic system may play in the disease, **exophthalmic goiter** (Graves's thyroid disease) is also associated with hypersecretion of the thyroid and that a large number of the symptoms are due to this cause. During the activity of Graves's disease the glandular parenchyma of the thyroid is hyperplastic, but later in the disease connective tissue is often formed and the hypersecretion ceases. In **adiposis dolorosa** the thyroid gland has been found abnormal, the secretion being probably diminished in most cases. It has been suggested that **paralysis agitans** and **myoclonus** have disturbed thyroid secretion as part of their pathology. Kashiwamuri, after examining fifty-five thyroids obtained at autopsies, states that the **connective tissue is increased in infectious processes.** This was notably true in cases of tuberculosis, diphtheria and typhoid fever.

There can undoubtedly be variations in the amount of thyroid secretion, from diminution sufficient to produce myxedema to the excessive secretion which characterizes Graves's thyroid disease, and many cerebral, vasomotor and cardiac disturbances may be due either to diminished or to excessive thyroid secretion. Disturbance of the secretion may also undoubtedly take place, so that some elements may be increased while others are diminished, and this may cause varying symptoms and affect the results of thyroid treatment in various ways.

Summary

To sum up the physiologic action of the thyroid gland, its secretion seems necessary for maintaining normal cerebral irritability and for regulating the circulation, nutrition and development of the brain; for maintaining the proper amount of mucin in the tissues, especially in connective tissue; for regulating the growth of connective tissue, especially in the skin; for the chemical organization of phosphoric acid (P_2O_5) for bone growth; for the regulation of the insensible perspiration; and for the regulation of the peripheral circulation and heat dissipation (thermolysis).

The gland is easily excited to oversecretion, temporarily by emotion,

and normally by menstruation and pregnancy. The periodic increase in the secretion of this gland in women is probably the cause of the greater frequency of Graves's disease in women than in men, the former having the disease four times as frequently as the latter. It is interesting to note that this gland undergoes abnormal atrophies to the point of causing myxedema also four times as frequently in women as in men.

The thyroid secretion usually begins to diminish after the age of fifty, and the gland becomes atrophied in old age. This diminution of physiologic function allows the blood-pressure to become higher as age advances; it is perhaps one of the causes of increased weight after forty and may account for the shrinking of the skin in senility and in some cases for the diminished brain power. The increased blood-pressure allowed by the loss of vasodilator stuff completes the picture of senility with the hardening of the arteries and the increase of connective tissue in the various organs.

Leichtenstern and Wendelstadt were probably the first to take therapeutic advantage of the physiologic fact that thyroid feeding increases the metabolism of the body by administering extracts of the gland to obese patients. Thyroid feeding causes a marked loss of weight, due largely to a diminution of the fat, and this loss continues for some time after the cessation of the treatment. All the symptoms of hyperthyroidization, such as palpitation, giddiness, syncope and even glycosuria, can be induced by such treatment.

In the normal individual a small dose will, as a rule, be but little noticed unless it is continued for a long period; but large doses of thyroid extract, thyroid glands, or iodothyrin may cause nausea, vertigo, palpitation, sweating, diuresis, cerebral irritability, faintness and tremor.

Parathyroids

A discussion of the thyroid gland is not complete without reference to the parathyroids, as without doubt some of the symptoms and conditions following thyroid extirpation are referable to the fact that the parathyroids have been more or less completely removed at such operations. Just what the parathyroids furnish to the organism as distinct from thyroid secretion has not yet been positively determined.

Although Sandström discovered these glands in 1880, they were forgotten until Gley in 1892 drew attention to them and reported that he had found them to contain iodin. Since this time there has been considerable experimentation having for its object a study of these glands. The number of parathyroids in animals has been found to vary, and MacCallum states that if all are removed, the animals rapidly die in con-

vulsions unless parathyroid extract be administered; that removal of the thyroid gland alone causes metabolic disturbances, wasting and chronic cachexia, while removal of the parathyroids alone after a few days causes twitching of the muscles, sometimes spasms, inco-ordination and partial paralysis of the legs, excessively rapid respiration, snapping of the jaws, and finally death from exhaustion. All of these symptoms are immediately relieved by intravenous injections of saline solution, but the improvement is only temporary. MacCallum considers this to prove that the toxin or toxins which cause the irritation of the nervous system are easily diluted or neutralized. Verstraeten and Vanderlinden have shown that parathyroidectomized dogs do not develop toxic symptoms so rapidly if they are kept upon a milk diet.

Although the function of the thyroid and that of the parathyroids must be physiologically correlated, still it is improbable that the parathyroids can ever perform the work of the larger gland. Accessory thyroid glands, however, may hypertrophy and do full thyroid work after the principal gland has become atrophied or been removed.

The facts so far ascertained in regard to the function of the parathyroid bodies are not sufficient to justify any exhaustive statement as to just what part these organs play in the economy. That they secrete something and belong to the list of ductless glands must certainly be conceded. MacCallum has conclusively shown that in their absence something irritates the nervous centers. They probably furnish some product that neutralizes some toxic substance in the blood or that forms combinations preventing the production of such an irritant. Unlike the thyroid gland, the parathyroids have but little to do with nitrogenous metabolism.

But little is known of the pathology of the parathyroid glands. Benjamins states that they are not changed in goiter, but that he has found them affected in general miliary tuberculosis. Edmunds believes they take some part in the pathology of Graves's disease.

Therapeutic Uses of the Thyroid Gland Substance and Extractives

Conditions in which the Thyroid Gland is Functionally Lacking

Cretinism cannot ordinarily be diagnosticated until the child is about six months of age, and if the thyroid gland is present and secreting at all, infantile myxedema cannot, as a rule, be diagnosticated until the child is three years of age. The gross appearance seen in cretinism needs no description here, but the diminished nitrogen metabolism in both this condition and myxedema should be remem-

bered, as positive indications of the success of treatment can be obtained by careful analysis of the urine. The majority of cretins may be expected to improve on thyroid treatment. At first the dose for an infant should be not more than five centigrams (about one grain) two or three times a day; the appearance of undesirable symptoms, such as increased cardiac action or loss of appetite, is an indication for the temporary withdrawal of the drug. Older children should be given correspondingly larger doses. According to Osler, if there be not considerable reduction in weight and improvement in the myxedematous condition of the skin within a month, the dose should be increased. When the treatment is successful, not only the body-weight is reduced and the appearance of the skin improved, but the mental powers are increased, bones and teeth grow, and the hair becomes more abundant and finer in texture. In a case associated with glycosuria Alfred Gordon observed disappearance of sugar as an early sign of improvement. After general bettering has been achieved, the treatment may be discontinued for a short time, after which, however, a small amount of thyroid extract should be given every week for a long period.

In **struma thyreopriva** or operative myxedema there can be no possible question of the advisability of thyroid feeding, and the only questions to be considered are the size and frequency of the dose. If symptoms of beginning myxedema appear in a patient from whom the thyroid has been removed, from twenty to thirty centigrams (three to five grains) of dried thyroid extract should be given twice a day. If the symptoms are not ameliorated in about two weeks, the dose should be increased; but after the disappearance of the symptoms the dose should be diminished by half, and after this dosage has been kept up for a short time the case should be treated on the same plan as a case of cured cretinism.

Myxedema.—In well-developed idiopathic myxedema, that is to say, a case not dependent on thyroidectomy but of toxic or other etiology, improvement from the feeding of thyroid extract will not be noticed for some time and large doses must often be given in individual cases. A dose of thirty centigrams (five grains) three times a day is not too large to begin with in a case of well-marked myxedema in an adult. In any case the patient should be seen at intervals of not less than a week, as it is always found necessary to vary the dose or interrupt the treatment altogether from time to time. The dose may have to be increased in certain cases to sixty centigrams (ten grains) in the twenty-four hours. It is probable, however, that the dose of thyroid extract employed in this as well as in other conditions has in many instances been too large, and it is well, while inaugurating treatment with the extract of any ductless

gland, to bear in mind how small an amount of secretion is furnished daily to the system by the normal gland. There are all degrees of diminution of thyroid secretion, from a condition characterized by slight apathy and the putting on of weight to actual myxedema. Hence the amount of thyroid extract needed to correct the condition present can be determined only by the symptoms and by the results of treatment. In most cases of **diminished thyroid secretion** a small daily dose of say five to ten centigrams (about one to two grains) is doubtless physiologically correct.

When symptoms of deficient thyroid secretion occur in **akromegaly,** thyroid extract in small doses should be administered, this disease having as part of its pathology disturbance of the thyroid gland. Headache and somnolence are sometimes relieved, and glycosuria has been observed to diminish or cease.

Goiter

The value of thyroid treatment in **goiter** can be determined only by a study of each individual case. If the enlarged portion of the gland has caused irritation of the rest of the gland and hence hypersecretion, as is sometimes the case, thyroid treatment is counterindicated, as it would produce symptoms of Graves's disease. If, on the other hand, the gland is so degenerated and cystic as to cause diminished secretion, small doses of thyroid are beneficial. As the size of the goiter frequently diminishes under any treatment, especially with iodin, to enlarge again and perhaps again to diminish, it is difficult to determine positively what the results of thyroid treatment are. Ordinarily large cystic or colloid goiters are not much affected by thyroid feeding unless such doses are given as to cause symptoms of thyroid intoxication. In these goiters other forms of iodin are as efficient in reducing their size and much safer, while in some instances operative treatment is indicated.

Graves's Disease

The pathogenesis of **exophthalmic goiter** (Graves's thyroid disease) is as yet undetermined. Dana believes that the primary disturbance is in the cerebral centers, and particularly those which control the nutrition of the thyroid and regulate the circulation. He does not say where these centers are located. Tedeschi states that lesions of the restiform body in rabbits and dogs will cause not only exophthalmos and tachycardia, but many of the symptoms of thyroid intoxication. Much of the pathology of this disease has also been referred to the sympathetic system. Blake calls it 'a stereotyped fear.' Whatever

the original lesion or disturbance, every case of Graves's disease during the continuance of active symptoms exhibits hypersecretion of the thyroid gland. During this period *thyroid feeding is counterindicated*, for all the symptoms—palpitation, tremors, nervous excitability, erethism, headache, sweating, flushing, sleeplessness and loss of weight—are increased by it. In most cases this disease tends to recovery; the increased secretion diminishes. Occasionally the thyroid gland becomes overworked by its excessive activity, degeneration sets in, connective tissue is formed and a diminution of secretion results. The symptoms then become those of a mild form of myxedema. In these cases *thyroid extract is indicated.*

As there may be all grades of diminished thyroid secretion, so there may also be **all degrees of oversecretion,** and symptoms of irritability, excitability, neurotic and hysterical manifestations may be due to increased secretion of the thyroid without apparent enlargement of the gland and without exophthalmos. Functional palpitation, sweating and hot flashes may be due to this same cause. It is important to be able to recognize these minor degrees of thyroid or vasomotor disturbance.

As thyroid secretion may vary in quality as well as in quantity, the working rule for thyroid treatment in exophthalmic goiter and other conditions of excessive or perverted secretion is that, in the presence of cerebral excitement, palpitation and progressive loss of weight, thyroid feeding is **counterindicated.** Should the patient be sleepy, apathetic and putting on flesh, thyroid extract may often be given in small doses with benefit, provided there is no palpitation or headache. S. Solis Cohen points out that the reaction of the patient to external temperature and cutaneous pressure is often a good clinical guide to the use of thyroid extract or of some antagonist, as suprarenal or thymus extract. When patients are unduly sensitive to slight degrees of atmospheric heat (75° to 80° F.), sweat unduly or develop dermographism or factitious urticaria with great rapidity, it is his experience that they are usually made worse by thyroid and benefited by thymus or adrenal extract. On the other hand, one who is unduly sensitive to cold weather or to cold applications (32° to 60° F.) or who is deficient in perspiration on exposure to heat, is usually benefited by thyroid extract. He points out in this connection a certain synergism between the action of thyroid-gland substance with that of ether, chloroform, alcohol and nitroglycerin; and an antagonism to digitalin, strychnin and atropin.

In 1894 Lanz began the treatment of exophthalmic goiter cases with the **milk of thyroidectomized goats.** This treatment met with sufficient success to stimulate others to use the same treatment, on the theory that

the milk of these goats would counteract the hyperthyroidization of the blood. As patients often rebel against the long-continued use of this goat's milk, a dried preparation of it has been made and is sold under the name of **rodagen.** The **dose** of this substance is from five to ten grams (one and a quarter to two and a half drams) a day, and improvement can be expected to take place in about two weeks. S. Solis Cohen, however, has observed in one case increase of thyroid swelling and greatly increased tachycardia, accompanied with excessive and causeless fear, as the result of this method of treatment; the symptoms subsiding upon withdrawal of the preparation and reappearing with its renewed use. Success has also been reported from the administration of **serum prepared from thyroidectomized sheep.** Merck offers a preparation of this serum under the name of **antithyreoidin,** the **dose** of which is large—as much as four and one-half grams (about one dram) three times a day. In passing, the frequent occurrence of **pigmentation** and of intermittent **glycosuria** in cases of exophthalmic goiter should be noted as showing the interrelation of the ductless glands.

Obesity

Obesity can almost invariably be reduced by thyroid treatment, but unfortunately the diminution of fat is accompanied by increased nitrogenous loss. In some cases this increased nitrogen metabolism is of advantage; in other cases it tends to weaken the patient. Most cases of overweight, especially in the very young and in patients over forty, can be reduced by larger or smaller daily doses of thyroid extract, provided there are no ill effects from the treatment. Personally I believe this treatment to be efficient, but to carry with it considerable risk of more or less persistent and troublesome debility. The initial dose should be twenty centigrams (three grains) two or three times a day, and this dose should gradually be increased to perhaps as much as sixty centigrams (ten grains) three times a day in order to get the best results. The patient may not begin to lose weight for the first two weeks; then, however, the loss progresses more or less rapidly from two to five pounds a week or even more, and he will continue to lose weight for some weeks after the treatment has ceased. The unpleasant symptoms caused by such large doses may be nausea, loss of appetite, frequent attacks of palpitation, weakening perspiration, at times coldness of the hands and feet, general muscular relaxation and debility, with possibly attacks of syncope. I have seen a convulsive attack, epileptoid in character, occur after the use of large doses of thyroid for obesity. During prolonged thyroid treatment the loss of weight may be very irregular, some weeks

showing no loss at all and other weeks bringing the loss up to the average. It is not necessary, in order to insure success, that the diet be modified, although such a course cannot fail to be beneficial. Whether the improvement will be permanent or not cannot be foretold. The majority of cases, especially those in which the obesity is hereditary, put on weight again after the treatment has been stopped, unless habits of overeating and inactivity have been corrected. Thyroid extract is often successfully used in reducing juvenile obesity. In conclusion, let me repeat that the treatment is attended with considerable risk and is to be used only when other methods are unavailable or unavailing, and then with the greatest care and caution.

Skin Diseases

Thyroid feeding increases the peripheral circulation, stimulates the sweat glands and possibly the sebaceous glands, hence improves the condition of the corium, and induces more rapid exfoliation of the epidermis. Thyroid is, therefore, indicated in **chronic** skin diseases, especially such forms as cause dryness of the skin or a scaly eruption, as **psoriasis** and **scaly eczema.** Some dermatologists dislike to use thyroid preparations because of the debility and loss of weight which they have observed to follow this form of treatment. Such untoward effects have generally been due to the use of excessive doses, and with due care good effects without undesirable symptoms can be achieved in most of the scaly eruptions. Thyroid is certainly a satisfactory remedy, when given in small doses, for the scaly eczemas of old age and for the **pruritus** that occurs in patients with dry skin. I have seen good results from small doses in young, flabby, strumous children who were prone to recurrent **cracks and fissures of the skin** in various parts of the body. Enlargement of the glands of the neck is often found in such children, and this condition may be relieved by small doses of desiccated thyroid, as five to ten centigrams (say one to two grains) a day.

Mental Diseases

Oversecretion of the thyroid gland, as in exophthalmic goiter, increases the cerebral irritability, causes excitation, or in some few instances mania. On the other hand, undersecretion causes mental hebetude, as in cretinism and myxedema. These facts have suggested to alienists the use of thyroid preparations in cases of **insanity.** It is rational to expect that a secretion which modifies, if it does not control, the circulation of the brain, which stimulates, and in excess irritates, the nerve-cells, might be given with good results in depressive functional

disturbances of the mental faculties, even though it cannot better cerebral degeneration. The prognosis of some cases of insanity can be made after a trial of this treatment. In cases of **hypochondriasis** and **melancholia** the brain needs to be stimulated; in such cases thyroid treatment seems to be indicated and is certainly sometimes beneficial. Hessler finds that there is always some nervous reaction to thyroid stimulation in the insane, though many cases respond only to large doses. When the treatment is discontinued, however, the sensory and motor activities in most cases again become depressed. He finds that **cataleptics** are permanently benefited, and says "apparently all that is required for the restoration to a life of normal activity in these cases is the stimulus derived from the substance of the thyroid gland." He has seen symptoms of exophthalmic goiter caused by large doses of thyroid.

It would perhaps be wise always to try thyroid treatment in **insanity of the menopause** and in **puerperal insanity,** as there is probably a functional disturbance of the thyroid gland at these times; although whether it is an oversecretion, an undersecretion or a perverted secretion has not been determined.

Uterine Disease and Disorders

I have already referred to the psychic disturbances of the **climacteric.**

That there is a **vasomotor ataxia** at the time of the menopause there can be no doubt, and this is largely due to a disturbance of the thyroid gland, the activity of which gland is closely associated with the menstrual function. If the thyroid, which has normally been oversecreting once a month, ceases its periodic oversecretion synchronously with the abolition of ovulation, the establishment of the menopause is attended by the minimum of constitutional disturbance. If, however, the thyroid continues to furnish at intervals an excess of secretion, hot flashes, palpitations, and the cerebral and nervous disturbances characteristic of this period are in evidence. If, on the other hand, the thyroid secretion diminishes too rapidly at the menopause, a condition of more or less pronounced myxedema develops. Eighty per cent. of all cases of myxedema occur in women. If women rapidly put on weight at this period and are not disturbed by symptoms of excessive thyroid secretion, small doses of thyroid extract are advisable. For the psychic and vasomotor disturbances occurring at the menopause, which I believe to be due to excessive thyroid secretion, *thymus gland* is sometimes of benefit, and any treatment found valuable in exophthalmic goiter will generally benefit these patients.

Dysmenorrhea.—Many of the nervous disturbances that occur in young girls before the full establishment of menstruation are, I think, due to increased secretion of the thyroid before such an increase is functionally needed, and this exaggeration of the thyroid function is probably one cause of the profuse menstruation that often occurs in neurotic girls. Such cases may well be treated with *thymus* or *mammary extract*. Dysmenorrhea caused by **spasmodic contractions of the uterus** or cervix and the variety that manifests itself by slow and painful establishment of each menstrual flow can often be avoided by administering thyroid substance for several days before the expected flow. In other words, thyroid extract is one of the best emmenagogs that we possess. Whether it can produce abortion has not yet been decided.

The treatment of **puerperal eclampsia** with thyroid extract has been much discussed of late. Whether it be an inference or a fact, the thyroid gland seems to undergo enlargement and its secretion appears to be increased during pregnancy. Certain it is that the mother's metabolism is increased during this process and a gland so closely associated with nitrogenous excretion, if undersecreting, might allow intoxication sufficient to cause eclamptic attacks. Nicholson thinks that deficiency of the thyroid secretion toward the end of pregnancy may allow a diminution of urinary excretion, leading to toxemia and finally to eclampsia. If these conclusions are correct, thyroid treatment is certainly indicated in the latter months of pregnancy if indications of deficient thyroid secretion are present. In this connection it may be noted that I have seen some cases of **functional epilepsy** benefited by thyroid treatment.

As there is a tendency at the time of the menopause or later to the development of **carcinoma** of the uterus, Bell suggests that the diminution of thyroid secretion after this period may be a cause of such epitheliomatous growths. He therefore administers thyroid to patients with carcinoma with reported good results. Thyroid treatment has also been used with some success against nonmalignant growths, especially **uterine fibroids.** It has also been said to promote the secretion of milk during lactation.

Symptomatic Uses of Thyroid Extract

S. Solis Cohen first reported symptomatic good results from the use of thyroid in certain cases of **nephritis,** some parenchymatous, but chiefly interstitial or mixed. It dilates the peripheral blood-vessels, increases perspiration and causes diuresis, perhaps by increasing the quantity of urea. Alfred Gordon has observed disappearance of sugar and symptomatic recovery from **diabetes mellitus** under thyroid feeding.

Fuller reports the successful use of thyroid extract in a case of serious **hemophilia.** This case was so positive and so conclusive that the use of thyroid in this condition should be further studied.

Administration

The injection of **glycerin extracts** of the thyroid gland first practised by Murray of Newcastle, England, was succeeded by feeding with the raw gland, and this in turn by the use of desiccated thyroid substance. The thyroid-gland preparations of commerce are mostly made from the thyroids of the sheep; the dried powder (*thyreoidinum siccatum* or *pulvis thyroidini*) and the tablets made with sugar of milk are the forms most used. The **dose** of the powder is from five to twenty centigrams (about one to three grains) one, two or three times a day, though to reduce obesity the dose must be much larger. The tablets contain two, three or five grains of the powdered thyroid. Two albuminoids have been isolated from thyroid substance, namely, thyroproteid and thyreoidin.

Iodothyrin is Baumann's preparation of the thyroid gland. It is a brown powder containing nine per cent. of iodin and one-half of one per cent. of phosphorus. The dose of this preparation is somewhat larger than that of the thyroid powder.

Rodagen is a preparation made from the milk of goats deprived of their thyroids; it is therefore an **antithyroidin.** A dried extract of this milk, triturated with 50 per cent. of milk-sugar, is marketed as a whitish powder the dose of which is from five to ten grams (75 to 150 grains) a day.

THYMUS GLAND

As the thymus gland atrophies in childhood and disappears after puberty, it probably plays some important part in the development and growth of the young child. If it have any other function, some other gland or glands must assume such work after the age of puberty.

Physiology and Toxicology.—Sudden death in young children has frequently been attributed to an enlargement of the thymus gland, causing sudden pressure upon the trachea and large blood-vessels of the chest when the head is thrown back. The pathology and toxicology of the lymphaticus or thymus death have not yet been satisfactorily worked out. The suggestion of sudden thymic intoxication has been made.

Dogs deprived of their thymus glands have shown a diminished growth of bone and hair, with leukocytosis. Frogs cannot live without the thymus gland, and before death exhibit loss of strength, palpitation, ulceration and hemorrhages.

But little is known of the **physiologic action** of thymus-gland preparations, although Svehla found that intravenous injections of extracts of this gland caused acceleration of the pulse in dogs by direct action on the heart and lowering of the blood-pressure by paralysis of the vasoconstrictors. Large doses may produce dyspnea, collapse and death.

Mendel has proved that the thymus gland both in man and in animals contains no iodin, and traces found in any given specimen are merely accidental, like traces found in any other part of the body outside of the thyroid. The thymus contains a large quantity of **nuclein** and hence a large amount of **phosphorus.**

The **pathology of the thymus** has been but little studied, and what relation some of the functional disturbances of infancy bear to this gland is not known; but rickets and some forms of marasmus are probably associated with, if not due to, undersecretion of the gland. Its secretion quite possibly aids in the formation of bone, which is produced so rapidly in the young child. In some cases of akromegaly and pulmonary hypertrophic osteo-arthropathy this gland has been reported as present, but only histologic examination is conclusive, as supernumerary thyroids have been found in the thorax. So-called strumous conditions in young children are perhaps more frequently caused by a disturbance of the thyroid than of the thymus function; but as there appears to be some normal balancing correlation between the two glands, disturbance of the one is likely to affect the other, and it is difficult to say which lesion in such cases is primary.

The thymus gland has been found absent in some cases of hemophilia, and in this connection it is interesting to note that thymus extract shows some coagulant action on blood.

Therapeutic Uses.—Until physiologists and pathologists give us more exact data, the use of thymus extract must be purely empirical.

F. Mendel administers it in **rickets** and finds that all the symptoms improve: the sweating diminishes, the bones grow stronger, dentition progresses, and attacks of *laryngismus stridulus* become fewer. His observations are based upon the study of 100 cases treated with thymus tablets given in soups.

There is a large mass of evidence that thymus treatment is often of value in **Graves's disease.** The **dose** should be from 10 to 30 centigrams (about two to five grains) three times a day. As there are no toxic or disturbing symptoms known or suspected to occur from the feeding of thymus, other than occasional gastro-intestinal irritation, larger doses might perhaps be given though it would be unsafe to say that there is no limit to the dose.

Thymus has been given for **simple goiter** and in many cases considerable success has been reported.

S. Solis Cohen recommends the use of thymus as a general tonic and especially in conditions of **vasomotor ataxia** of the relaxing variety, as seen in patients who have marked relaxation of the blood-vessels in summer, perspire easily and are very sensitive to heat. He recommends thyroid for the opposite condition—namely, for patients who suffer from cold in winter. I have already mentioned (page 83) the use of thymus for the nervous disturbances at the *menopause* and at *puberty* dependent upon excessive, perverted or premature thyroid secretion.

As thymus secretion is a tissue builder, it must have something to do with the formation of bone salts. As these earthy salts are necessary for the permanent encapsulation and healing of tuberculous lesions of the lungs, the extract seems indicated in **tuberculosis,** and I have found most cases of pulmonary tuberculosis benefited by thymus feeding. In this connection Tissier's observations on the hypotension of phthisical and hypotrophic persons may likewise be recalled (See Volume x). Clinically thymus feeding improves lowered vascular tone in adult man, though experimental observations show an opposite action on animals under laboratory conditions. The contradiction is unexplained as yet.

Infantile atrophy and unexplainable **infantile marasmus** may be due to insufficiency of thymus secretion. As the extract is always tonic and probably never debilitating, it should be given in these cases.

In **hemophilia** and in **scurvy** thymus feeding may do good.

As the thymus is rich in nucleins and phosphorus, it can be substituted for any nuclein treatment desired.

Administration.—Thymus preparations are made from the thymus glands of sheep and pigs, and are marketed in powder and tablet form. The **dose** is from 5 to 20 centigrams (about one to three grains) two or three times a day. Unlike thyroid gland, thymus can do no harm in any ordinary dosage. It is a tissue builder and not a promoter of nitrogenous waste. As a physiologic hemostatic, Wright commends for local use the following: Fresh and finely minced thymus is extracted from twelve to twenty-four hours with from ten to twenty times its weight of a solution containing one per cent. of carbolic acid and one per cent. of sodium chlorid; and to this is added, after straining, 0.5 per cent. of crystallized calcium chlorid. It is then made faintly alkaline, shaken and mixed with the effused blood, in the proportion of about 1 to 10.

PITUITARY GLAND

The pituitary body consists of an anterior lobe, the *hypophysis cerebri*, and a posterior lobe, the *infundibulum;* but these lobes are of different structure. The anterior lobe is distinctly glandular, while the posterior lobe contains a few glandular cells and a number of nervous elements. The histologic appearance of the anterior lobe resembles that of the thyroid, and the functions of the hypophysis and thyroid are closely correlated, as shown in akromegaly and in some cases after thyroidectomy. Sajous thinks that the anterior pituitary body governs the activity of the adrenals,—being connected with the latter through the sympathetic nervous system,—and believes that there is a close relationship between the functions of the thyroid, the suprarenals and the pituitary. He states that iodin, in the organic combination in which it occurs in the thyroid, is a stimulant to the pituitary, while the secretion of the latter in turn increases the activity of the adrenals.

Physiology and Pathology.—It has been observed that when this gland is removed from cats and dogs, death occurs with symptoms not unlike those of thyroid extirpation and that the symptoms are mitigated by injections of pituitary extract. Other experimenters have kept animals alive for months after extirpation of the hypophysis. The symptoms of total extirpation have been motor disturbances, depression and emaciation. Howell showed, in 1898, that injections of extract of the infundibular part of the gland raised the blood-pressure and increased the heart action, but this action was much less marked than that produced by suprarenal substance. The vasoconstricting action on the blood-vessels from this infundibular substance is a peripheral one and is due to its secretion and not to an extract of the nervous tissue. Injections of the secretion from the hypophysis cause a slowing of the heart by prolongation of the systole, even after division of the vagi.

The pituitary body is probably always oversecreting in **gigantism** and furnishing diminished or perverted secretion in **akromegaly.** I believe that akromegaly often begins as gigantism and will so manifest itself if the increased secretion of the pituitary begins before the age of twenty-five or before the hypophyses have become firm bone. After complete ossification of the skeleton oversecretion will develop the appearance of akromegaly. Sooner or later, in most cases of gigantism and akromegaly, the pituitary becomes degenerated and undersecretes, or its secretion is entirely abolished, and the manifold conditions and symptoms of advanced akromegaly appear.

In the first stage of akromegaly there is increased hard-bone forma-

tion, the extremities grow, the cartilage around the joints and the tendons of the muscles ossify and exostoses form; while in the latter stage there is often distinct thinning of the shafts of long bones and of the flat bones. Small doses of phosphorus may increase bone structure, while large amounts of phosphorus will cause thinning of bones; hence it would seem that in akromegaly there may be too much physiologic phosphorus in the system. In well-marked cases of akromegaly the pituitary is generally found in an adenomatous or sarcomatous condition or in a state of cystic degeneration. Reported cases of tumor growths of the *sella turcica* without symptoms of akromegaly have probably had normal secretion furnished by some portion of this gland or some accessory pituitary.

The pituitary gland has been found diseased in **pulmonary hypertrophic osteoarthropathy.**

Therapeutic Uses.—Special symptoms attributed to the feeding of pituitary, except a bettering of the circulation, have not been noted. It may be found of value in cardiac debility and when the blood-pressure is low; but as its action is inferior to that of suprarenal preparations, it cannot supersede the latter in cases of circulatory debility.

Extracts of pituitary glands have been employed in **akromegaly** with varying and uncertain results. The treatment should certainly be tried, however, in every case, at the first appearance of symptoms of debility or functional disturbances. I have seen the severe akromegalic headache disappear, mental ability increase, muscular strength improve, depressed arterial tension become raised and myxedematous puffing of the lips and hands diminish under pituitary treatment. Whether or not pituitary and thyroid can ever be used interchangeably has not been decided. Thyroid is not ordinarily good treatment in akromegaly. It is quite probable that if pituitary treatment were to be given in the first stage of akromegaly or in gigantism, the condition would be aggravated.

Administration.—Pituitary preparations are made from the pituitary bodies of the sheep and are offered in powder and tablets. The **dose** is from 5 to 20 centigrams (about one to three grains) two or three times a day. Perhaps larger doses would often be of value in the later stages of akromegaly.

SUPRARENAL GLANDS

Before considering the suprarenal glands and the results caused by their removal or disease, brief mention should be made of the little adrenal bodies found along the spermatic vessels in the male and within

the broad ligaments in the female. Whether or not these glands are always present has not yet been definitely decided; but their full development might readily modify the symptoms to be expected from extirpation or disease of the adrenal glands and account for some of the discordance of experimental results and the discrepancies between clinical conditions and pathologic findings. Warthin has suggested the name "adrenals of Marchand" for these little supernumerary or auxiliary glands.

Physiology and Pathology.—Radasch calls attention to the fact that the suprarenal glands are frequently misplaced. Addison in 1855 pointed out the relationship between disease of the suprarenal capsules and anemia with brown pigmentation of the skin and mucous membranes. One year later Brown-Séquard showed that removal of the suprarenal bodies was fatal, the animals dying apparently from paralysis of the respiratory muscles after showing symptoms similar to those seen in shock. He also stated that the administration of suprarenal substance, either by the mouth or hypodermatically, prolonged the life of these animals but did not prevent death. Since that time it has been proved that death always follows rapid extirpation of these glands unless supernumerary adrenals are present. After complete ablation death occurs too soon for pigmentation of the skin to take place; but if the glands are injured, as by crushing, or if the suprarenals of rabbits are inoculated with tubercle, symptoms similar to those of Addison's disease develop. Schäfer and Oliver first showed that the adrenal glands contain an element which, when injected intravenously, strengthens and slows the heart and raises the blood-pressure more than any other known substance. They also showed that this pressor element is contained only in the medulla of the gland and extracted by water.

In 1897 Abel isolated from the adrenal gland an active ingredient which he termed **epinephrin.** This isolated substance, according to Moore and Purinton, does not increase the blood-pressure to the same degree as a crude extract of the medulla of the gland. In 1900 Fürth isolated a substance which he termed **suprarenin,** but which Abel says is identical with epinephrin. Still later Takamine isolated a substance which he states to be from 600 to 1000 times more active in raising the blood-pressure than an extract of the fresh gland, and this substance he named **adrenalin.** Aldrich confirms Takamine's belief that adrenalin is the active principle of the suprarenal substance; but Abel believes that "adrenalin is very probably chiefly a mixture of native and reduced epinephrin containing traces of foreign substances rich in nitrogen."

Batelli, from his examinations of the adrenals of animals and human beings, finds that the normal adrenalin content is from 7 to 12 centigrams to 1000 kilograms of body weight. This, however, is no index to the quantity secreted in a day or circulating at any given moment.

Moore and Purinton found that very minute doses of suprarenal extract cause a fall in blood-pressure instead of the customary rise produced by ordinary doses. They also found that the suprarenals of the young fetus contain no active pressor substance.

But little if any change in the blood-pressure takes place when suprarenal substance is taken into the stomach; such effects are, however, readily produced by absorption from the buccal or other mucous membranes. Boruttau says the function of the suprarenals is to render innocuous the products of muscular activity, to regulate the nutrition of the muscular system and to control the blood-pressure so as to protect the brain and spinal cord from anemia.

The affinity of the suprarenal secretion for **oxygen** has been pointed out by Cybulski, Moore, Abel, Takamine and Sajous. Sajous proposes the name **adrenoxin** to designate the substance in suprarenal secretion to which this affinity for oxygen is due; he believes that this causes the carbon dioxid to be forcibly expelled into the air vesicles of the lungs and that the red blood-corpuscles, by taking up this oxygen-laden fluid, convert the hemoglobin into oxyhemoglobin. Sajous also believes that the anterior pituitary body governs the activity of the adrenals through the sympathetic system and that the hypophysis is in turn stimulated by the physiologic iodin formed by the thyroid. He thus has a triad of glands furnishing internal secretions, each one necessary to the successful functionating of the other two.

S. and C. Meltzer think that local applications of suprarenal solutions may be of **diagnostic value** to determine the efficiency of the sympathetic innervation of a part by the normal or abnormal reaction of the blood-vessels. In the absence of sympathetic innervation the usual vascular contraction fails and there may be dilatation instead.

Meltzer has likewise shown that adrenalin has the power to **delay both absorption and elimination** of toxic and other substances administered by the stomach, hypodermatically or into a vein.

Oppenheim believes that he has demonstrated an **antitoxic property** in solutions of the adrenals.

Bjelaventz sums up the **physiologic action** of suprarenal extracts as an elevation of blood-pressure by contraction of the blood-vessels and stimulation of the heart. The vessels are contracted by stimulation of the muscular walls. The pneumogastric center is first irritated and

then paralyzed; but the extract does not act on the vagus endings. Oxygen and carbon dioxid exchange is increased by small, diminished by large, doses. On the central nervous system it acts as a depressant, and death is caused by paralysis of the respiratory center. Bjelaventz cautions against the continued use of suprarenal when the pulse and respiration become rapid and I have seen harm from pushing such treatment too far.

Herter and Richards first called attention to the relationship of the suprarenals to **glycosuria.** The injection of adrenalin into the peritoneal cavity was followed by glycosuria and later examination showed degeneration of the islands of Langerhans in the pancreas. Subcutaneous injections of adrenalin occasionally produced the same results. The glycosuria caused by peritoneal injections of adrenalin reaches its height in a few hours and usually lasts less than twenty-four hours. The cause of this glycosuria seems to be overtaxing of the oxidizing powers, and consequent degeneration of the islands of Langerhans, too much reducing substance being offered to the pancreas at one time. Herter later showed that when the pancreas is extirpated four days after ligation of the suprarenal vessels on one side of the body and removal of the suprarenal gland on the other, no glycosuria occurs. He also produced glycosuria by massage of the suprarenals. Blum, Zülzer and Croftan have all given experimental proof that the suprarenals have something to do with sugar production and with glycosuria.

The literature of the relationship of **Addison's disease** to the suprarenals is large. Although it is probable that no case of true Addison's disease occurs without diseased adrenals, tumors and complete degeneration of these glands may occur without the supervention of the Addisonian complexus; it is quite possible, however, that in these cases the presence of supernumerary adrenal glands prevents the occurrence of the symptoms of loss of adrenal function. It is interesting to note that in Addison's disease with complete degeneration of the suprarenals an extract of these glands is devoid of power to raise blood-pressure.

Sergent describes symptoms which he attributes to **"acute adrenalitis."** These symptoms are pain in the lumbar and spinal regions, vomiting, diarrhea and prostration. Whether or not the diagnosis of such a condition can be made, it is quite probable that acute insufficiency of the suprarenals is one of the causes of shock and depression in acute infections.

Therapeutic Uses.—Bates was one of the first to point out the powerful **astringent** and **hemostatic** properties of the aqueous extract of desiccated suprarenal substance as shown by its action when instilled into

the eye, the palpebral and ocular conjunctivæ becoming blanched in a few minutes. Not even cocain can produce such an astringent effect, and this action is manifested by solutions of even less than one per cent. in strength. A fraction of a drop of a 1 : 10,000 solution of adrenalin or suprarenalin will blanch the conjunctiva in less than half a minute. Lest irritation be caused in the eye, only fresh, watery extracts of suprarenal substance should be used, or adrenalin or suprarenalin solution. Adrenalin is slightly irritant as it is very faintly acid, while suprarenalin is neutral.

Local Application.—The local treatment with suprarenal preparations is serviceable in all inflammations of the **eye**—conjunctivitis, keratitis, iritis, choroiditis, ulcerations, and even in glaucoma and neuritis. Applications should be made frequently and freely. In conjunctivitis it may be well to follow the application of adrenalin with a weak antiseptic wash; the inflammations may in this way be aborted. In lacrimal troubles and in operations on the eye suprarenalin or adrenalin solutions are valuable. The drug is both advocated and condemned in acute glaucoma. If used at all in this condition, care and judgment are evidently necessary. De Schweinitz says that a preliminary instillation of suprarenal solution enhances the action of cocain, atropin, eserin and pilocarpin.

Swain, in advising the local use of suprarenal in the **nose,** says "it is a powerful vasoconstrictor and contractor of the erectile tissue; it is perfectly safe* even in considerable quantities, and causes, even on frequent repetition, no vicious habit either in the tissue or in the individual; it enhances the effects of any drug used locally at the same time." It has its best use in the nose in acute inflammations, in hay-fever, in operations on the nose and in cases of epistaxis independent of causation. It is best applied to the nostrils, as a rule, by gentle spraying with a prepared, filtered, *aqueous solution of the dry powder.* In some cases application by means of a cotton wad is preferable. Suprarenalin and adrenalin solutions are also much used and are much easier to prepare. Only weak solutions should be used for the first time, as it occasionally causes considerable nasal irritation in patients who have an idiosyncrasy against the drug.

In all acute inflammations of the **tonsils, pharynx** and **larynx** spraying with suprarenal solutions tends to relieve congestion and to diminish and sometimes abort the inflammation. Follicular tonsillitis can

* The editor, however, has reported a case in which edema of the palate and pharynx followed the excessive use of suprarenal spray in the nose and throat.

often be aborted by first cleaning the tonsils with saline solution, swabbing with solution of hydrogen dioxid, and then spraying several times with suprarenal solution, repeating this treatment in about twelve hours. Some observers, however, have noted greater readiness to succumb to morbific influence in parts to which adrenalin has been applied and caution against its application in the throat when there is any suspicion of diphtheric or severe streptococcic infection.

In **angioneurotic edema** affecting the tongue or larynx suffocation may be imminent; indeed, instances of death from such a cause have been reported. S. Solis Cohen has observed prompt relief from the local use of adrenal preparations. They are less certainly efficient in **edema of the glottis** from other causes, but should be tried after the free bleeding of scarification or when scarification is not practicable.

The congestive stage of **acute urethritis** may be treated with advantage by suprarenal injections. In **strictures** of the urethra a local application of this vasoconstrictor will often diminish obstruction sufficiently to permit the passage of sounds and catheters. In chronic prolonged urethritis, when the mucous membrane is flabby, injections of suprarenal are sometimes of value. It has been used in **cystitis** and to stop **hemorrhage from the bladder.** Chassaignac advises its use to locate the source of hemorrhage in cases of hematuria; as hemorrhage from the urethra or bladder can be arrested by injecting suprarenal extract. In bladder bleeding he washes out the bladder with boric acid solution and then fills it with adrenalin chlorid solution, 1: 20,000, allowing the solution to remain in the bladder for about five minutes. If the bleeding continues, he repeats the injection of adrenalin.

Injections of suprarenal solutions into the prostatic urethra for **prostatic congestion** and inflammation are of value.

Meara reports successful treatment of **hyperemia and pruritus of the vulva** with local application of strong suprarenal solutions, the relief obtained lasting many hours.

In **postpartum hemorrhage** suprarenal solutions have been injected directly into the uterine cavity, which should be washed out soon afterward, as the solution rapidly undergoes decomposition. It is asserted that adrenalin solution or suprarenal powders, when absorbed in the mouth, will cause **active contraction of the uterus,** and Campbell has given with success 15 drops of adrenalin chlorid solution, 1: 1000, three times daily, for profuse **uterine hemorrhage** due to polypi and fibroid tumors. The editor has found it of use, in conjunction with other measures, in restraining persistent leakage of blood from an enlarged, flabby, virgin uterus which had previously been submitted unsuc-

cessfully to curetment and to amputation of the cervix. The patient is of the vasomotor-ataxic type.

In hemorrhages from **gastric ulcer** and **gastric cancer** strong solutions should be used. The drug is swallowed, but the application is topical, as the pressor principle is not absorbed from the stomach. In **atony of the stomach** adrenalin or suprarenalin solutions may be given for their useful local effect on the gastric musculature. MacDonogh of North Wales reports the successful treatment of **intestinal hemorrhage** by high rectal injections of adrenalin solution, 1:1000.

Lehmann suggests a preliminary injection of adrenalin solution into a region **to be operated upon** as a preventive of hemorrhage. He has experimented on animals and found that he could remove a lobe of the liver after such preparatory treatment. It produces some local anesthesia, and if combined with cocain, permits the latter to be used in larger quantity by retarding or even preventing absorption. This is said to be especially evident in the practice of **spinal anesthetization.** Thus it is found that after subdural injection of eight drops of the ordinary adrenalin solution as much as a grain and a half of cocain can be injected into the spinal canal of animals without any bad effect—that is to say, five times an otherwise fatal dose. These results have been confirmed in human surgery.

James Barr injects a dram or two of adrenalin solution, 1:1000, into serous cavities from which passive or inflammatory **effusions** have been removed. He believes that he has thus prevented reaccumulation of fluid in cases of pleurisy, hydrothorax, pericarditis and ascites.

Internal Administration.—Although suprarenal solutions yield such uniformly good results when applied locally, their administration by the stomach is not followed by satisfactory action on the heart and blood-vessels, as the pressor substance is not absorbed. Satisfactory action on the circulation is, however, obtained when solutions are absorbed from mucous membranes or the powder is chewed and allowed to absorb in the mouth. By this method **heart failure, shock** and **vasomotor debility** may be treated satisfactorily. Perhaps no drug is a better stimulant in such conditions. Floersheim recommends that capsules containing the powder be thoroughly chewed in the mouth and then swallowed without water, and after observing 200 cases, he finds that a circulatory reaction takes place in less than five minutes; sometimes he noted the action in fifteen seconds. The effect lasts from a few minutes to an hour, rarely much longer. Not only is this treatment valuable in acute cardiac failure, but I have found it of marked value in the **cardiac weakness of fever,** as typhoid. When the heart begins to

fail, I administer five drops of suprarenalin solution in half a teaspoonful or less of water every three hours or oftener as the case may require. This treatment should not be continued too long, but be stopped as soon as the circulation is improved, to be again resorted to when needed. The editor advises the use of his tablet triturates of suprarenalin upon the tongue in such conditions, especially in **pneumonia** and after **surgical procedures.**

Internal hemorrhages and **hemoptysis** may occasionally be successfully treated with suprarenal extract; absorption should take place from the mouth. Injections into the parenchyma of the lung have been made.

S. Solis Cohen has several times reported the successful treatment of **vasomotor asthma** with suprarenal preparations; the paroxysms becoming less intense and recurring less frequently. He administers suprarenalin powder in three to five milligram (one-twentieth to one-twelfth of a grain) doses, with a little sugar of milk, preferably by the use of very small tablet triturates. They are to be placed on the tongue and allowed to dissolve there—not to be swallowed. In an acute asthmatic attack he first sprays the nostrils with suprarenalin solution, which gives immediate relief, and then gives one of these powders from every ten minutes to every hour or two, to prevent a return of the paroxysm. **Hay-fever** he treats similarly; spraying with suprarenalin solution, or insufflating a powder of suprarenalin and boric acid (1 : 100), or inserting a "nasoid" containing $\frac{1}{20}$ grain of suprarenalin in a mass of cocoa-butter suitably shaped. Adrenalin ointment may also be used. Bullowa and Caplan report the relief of asthma by hypodermatic injections of adrenalin in doses of five to ten minims of the 1 : 1000 solution.

Suprarenal extract has been advised by Cohen in **exophthalmic goiter.** Care must be taken to obtain absorption of the pressor substance, namely, by allowing the drug to be absorbed from the mouth. Some observers, among whom I am to be numbered, have obtained but partially successful results or have failed entirely. The editor, however, has seen undoubted benefit, and in several cases recovery, due to the treatment. When used in conjunction with other measures, as, for example, the administration of thymus extract, he has observed it to hasten the good results. He uses suprarenalin also in conditions of relaxing **vasomotor ataxia,** both locally and by buccal absorption—for example, in urticaria, recurrent erythema, erythema nodosum, angioneurotic edema, membranous enteritis, pseudo-appendicitis, pseudorenal colic, hematuria and other visceral crises, and in incipient or atypical cases of Graves's disease.

In **Addison's disease** I believe suprarenal extract should always be

administered; the **dried substance of the gland** is preferable to any one active principle, as in this disease the entire internal secretion of the adrenals is diminished. Though the treatment is often unsatisfactory, successful cases are being reported. The **dose** should be from 10 to 20 centigrams (one and one-half to three grains) three times a day.

I have seen the output of sugar, diacetic acid, acetone and ammonia all decrease under suprarenal treatment in **diabetes** and would suggest its trial in cases apparently not due to disease of the pancreas.

Engman and Loth recommend the internal administration of suprarenal gland in general **pruritus** and in chronic **urticaria.** In **Schönlein's disease,** in **purpura** and in **scurvy,** as in **hemophilia,** the reports are contradictory; but the treatment should always be tried.

To sum up, a **strong aqueous solution** of suprarenal substance, suprarenalin or adrenalin should be used on any bleeding capillary surface that can be reached, as the stomach, large intestine, bladder, urethra, vagina and uterus, or for any congested mucous membrane, bleeding cancer and the like, or in angioneurotic edema of the tongue or air-passages. Suprarenal solution or suprarenalin powder should be given **for absorption in the mouth** to check internal hemorrhage and to combat shock, vasomotor paresis or cardiac asthenia. Suprarenal powder may likewise be used for local effect on the mucous membrane of the air-passages. In urgent cases, as of **cardiac collapse** in pneumonia, or in **chloroform or ether poisoning,** strong solutions of adrenalin or suprarenalin should be injected under the skin, or even drop by drop into a vein.

It has been suggested that suprarenalin or adrenalin would be of advantage in **morphin** and **opium-poisoning,** as these drugs tend to diminish internal secretion and the final collapse may be due to interference with the function of the suprarenal glands. Meltzer's recent observations on the delay of absorption brought about by suprarenal treatment suggests that in urgent cases of poisoning the method may be employed to gain time for the administration of chemical and physiologic antidotes. The concomitant retardation of elimination must, however, be kept in mind.

Reasoning by analogy from what is known of the action of the thyroid gland, suprarenal secretion may be decreased sufficiently to produce Addison's disease and increased sufficiently to cause persistent high tension, and between these two extremes there may be all degrees of decreased and increased secretion, giving symptoms which are now not understood. It is possible that the oversecretion of this gland is one of the causes of general **arteriosclerosis** and **gout.** The administration of **small doses** of *thyroid extract,* not sufficient to produce much loss of

weight, I have found to be a physiologic **antagonist** of much value in these conditions in preventing the progress of trouble from high blood-pressure.

Administration.—Suprarenal preparations are made from the suprarenal capsules of sheep and cattle. For **local application,** when the astringent and hemostatic effect is desired, the best preparations are suprarenal substance in the form of a powder or watery extract, and solutions of the active principle of the gland.

A number of suprarenal preparations said to keep indefinitely are offered for sale by pharmaceutic chemists; but none of these acts quite as satisfactorily as a fresh watery solution. As preservatives, carbolic acid, boric acid, resorcin, and chloretone are used. Strong and even weak alkalis destroy the active principle of the preparation.

Suprarenal substance is offered in dried powder and in tablet form.

Epinephrin is the active pressor principle of these glands, isolated by Abel. This is offered for general use by a pharmaceutic firm under the name of **suprarenalin** and occurs both in powder and in a solution of one part to a thousand. It is neutral in reaction and therefore nonirritant to mucous membranes.

Adrenalin, Takamine's isolated principle, is a white, minutely crystalline substance, mildly bitter, permanent when dry, readily soluble in hot, and slowly in cold, water. After a time, or when exposed to the air, adrenalin changes from white to pink and then to a brown color. Adrenalin is also furnished in the form of a **chlorid,** in solution of one part to one thousand of standard sodium chlorid solution, with a small quantity of chloretone as preservative. This preparation is slightly acid. Tablets of **adrenalin tartrate** are made that are readily soluble in water.

Neither suprarenalin nor adrenalin solution is quite so astringent or hemostatic to mucous membranes as a freshly prepared watery solution of the suprarenal powder; both are sufficiently active for all purposes for which suprarenal is used topically, except, possibly, in operative work. Both deteriorate with exposure to light and air; hence they must be dispensed in dark bottles containing small quantities, and kept well-stoppered.

The **strength** of solutions of the desiccated gland substance should be from eight to fifteen per cent. (five to ten grains to the fluidram) for use on mucous membranes. Adrenalin and suprarenalin solutions are used in **strengths** varying from one part in twenty thousand or ten thousand to one part in three thousand, one part in one thousand, or even higher, according to the exigencies of the case, as has been fully explained in the paragraphs on therapeutic uses.

When given for its **action on the circulation,** suprarenal extract must always be absorbed from a mucous membrane, because, when the preparation is taken into the stomach, the heart and vasomotor stimulation is lost. The **dose** of suprarenalin to be given in this way is from one to six milligrams (one-sixtieth to one-tenth grain) in triturate, or five drops of the 1:1000 solution, given from every ten minutes to every three hours. The solution may be placed on the tongue or instilled into the conjunctival sac. Positive action has also been obtained by giving **minute doses** of suprarenal solutions **hypodermatically;** but great care must be taken lest abscesses form, and this use of suprarenal should not be carelessly instituted. In dire conditions of collapse, **drop-by-drop instillations** of a very weak solution **into a vein** may be justifiable and would probably prove successful. The **dose** of both intravenous and hypodermatic injections must be carefully gaged, as cases of severe intoxication have been reported. In using watery solutions of the extract it should be remembered that decomposition takes place ordinarily after twenty-four hours, hence fresh solutions should be made daily.

For **systemic action** other than on the circulation the dried gland substance may be administered internally in the usual way. The **dose** of the dried gland is from ten to twenty centigrams (one and one-half to three grains).

CHAPTER II

ANIMAL EXTRACTS AND SIMILAR AGENTS OF MINOR IMPORTANCE

Pancreas. Spleen. Testicles. Ovaries. Mammary Glands. Parotids. Prostate. Nuclein. Brewers' Yeast. Lecithin. Glycerophosphates. Muscle Tissue. Red Bone-marrow. Gastric Juice. Duodenum (Secretin). Brain. Lymph Glands. Kidneys. Liver. Mucous Membranes (Mucin). Trunecek's Serum. Transfusion.

PANCREAS

According to Opie, the pancreas consists of two separate secreting elements, one connected with the ducts and furnishing its digestive secretion, the other element furnishing secretion to the blood by absorption into the blood-vessels, as in the case of ductless glands. Opie states that small displaced nodules of pancreatic tissue frequently occur either in the walls of the stomach or in the upper intestine. These accessory glands probably account for the clinical observation of tumors of the pancreas without diabetes.

Physiology.—In 1889 von Mering and Minkowski showed that in the dog and cat complete removal of the pancreas was always followed by **diabetes;** Schäfer has shown that removal of the pancreas is immediately followed by increase of sugar in the blood and its appearance in the urine, while at the same time the glycogen of the liver disappears. If a portion of the pancreas is left to the animal, diabetes will not occur unless this remaining portion becomes diseased. Herter (see page 91) has shown that after ligation of one adrenal and ablation of the other the pancreas may be removed and glycosuria not occur.

Recent investigations show that while the **pancreatic juice** is an active element in the absorption of fat, the bile is a more or less efficient substitute for the pancreatic juice in this work when the pancreas is diseased. Fatty diarrhea, though often caused by pancreatic disease, can occur without pancreatic disturbance; nor does disease of the pancreas always cause fatty diarrhea. Rapid and profound emaciation without apparent cause should always arouse the suspicion of degeneration of the pancreas, even in the absence of glycosuria. The islands of

Langerhans doubtless furnish the internal secretion of the pancreas, as was pointed out by Soboleff and by Herter in his experiments on suprarenal diabetes. That emaciation is not always a symptom of diabetes may be due to the fact that the islands of Langerhans are not diseased.

Zaremba suggests that the pancreas may have an **antitoxic influence** over toxins and poisons somewhat similar to that of the liver.

There is no question that disease of the pancreas sufficient to cause great diminution or abolition of the internal secretion leads to diabetes; but it is more difficult to account for the cases of diabetes without disease of the pancreas. However, there may always be some disturbance of the pancreatic function. Adami suggests that there may be an accumulation of sugar in the system beyond the transforming power of the pancreatic internal secretion, and hence incomplete burning up of the sugar due to relative pancreatic insufficiency. This is quite probably the condition in those cases in which the dietetic treatment of glycosuria is curative. When there are tumors in the pancreas without diabetes, it is probable that other portions of the gland are oversecreting or that supernumerary glands are doing the work.

Chittenden states that complete loss of the pancreas leads to much more than a mere disturbance of the relation between sugar and glycogen formation, and that some forms of pancreatic diabetes are due to the physiologic disturbance of the interrelationship of several glands rather than to a simple disturbance of the pancreas. Reference to the discussion of experimental glycosuria in the description of the suprarenal glands will explain this statement. It is also a fact that glycosuria is a frequent complication in disturbances of other internal secreting glands, as in Graves's thyroid disease, myxedema and akromegaly.

Therapeutic Uses.—The first treatment in **glycosuria** should be the dietetic, so as to ascertain the capacity of the pancreas for properly disposing of sugars and carbohydrates. If, under rigid diet, sugar continues to be thrown off by the kidneys in considerable quantities, it seems justifiable to infer that there is serious impairment of the internal secreting power of the pancreas and pancreatic extract should be given. The **dose** should be from 20 to 30 centigrams (three to five grains) three times a day, best given two hours after meals. The value of such treatment must, of course, be due to the internal secretion that it represents, as the digestive portion is quickly rendered inert by the acid or acid peptones in the stomach.

Soboleff suggests feeding to diabetics the pancreas of new-born

calves because the pancreas in these young animals has well-developed islands of Langerhans, although the glandular tissue is scarcely formed.

Modification of the diet in **intermittent glycosuria of Graves's disease** and **akromegaly** is generally curative.

Salomon reports two cases of pancreatic glycosuria with fatty stools in which the amount of fat in the feces was greatly decreased by the feeding of pancreas. The editor failed to influence favorably the course of pancreatic diabetes in two cases in adolescents, either by feeding with pancreas or by the hypodermatic use of a pancreatic extract.

It is possible that some cases of chronic diarrhea are due to imperfect action of the pancreas; at least some cases without symptoms of inflammation are improved by the administration of pancreatic extract.

Administration.—The pancreas is administered in powder, capsules, or tablets. The dose proper for any given condition has not been determined. For the sake of preserving the digestive power of pancreatin in the intestine a combination of pancreatin with tannic acid is offered under the name of **pancreon.** This substance is not affected by the gastric juice.

Its **dose** is 30 to 50 centigrams (five to eight grains) three times a day.

SPLEEN

The spleen can be removed from animals and man without producing serious results; but whether the function of this organ can be performed by lymphatic glands is still undetermined.

Physiology.—The function of the spleen is to produce leukocytes and perhaps lymphocytes, and to retain or destroy dead or diseased erythrocytes. It also has something to do with hemoglobin formation and under certain conditions may perhaps produce new red corpuscles. Schäfer suggests that it may serve as a reservoir at certain periods of digestion for the blood which has to pass through the portal system. The spleen undergoes regular rhythmic contractions and dilatations which may aid the portal circulation. Heinz believes that the function of the spleen in destroying red corpuscles can be performed in its absence by the bone-marrow and lymph glands.

Morphologically the spleen is a lymphatic gland and is readily affected when other lymph glands are diseased; hence it is enlarged in many of the acute infections. Extirpation of the spleen is followed by hypertrophy of other lymph glands and sometimes by enlargement of the thyroid and an enormous lymphocytosis.

Mendel and Rettger, in experimenting on the interaction of the pancreas and spleen, have shown that extracts of the spleen prepared

during digestion, as well as injections of defibrinated blood from the splenic vein, increase the proteolytic power of the pancreas. This bears out the hypothesis of Schiff and Herzen that the spleen furnishes an internal secretion capable of transforming trypsinogen into trypsin. Sylvestri has found that blood from the splenic vein will increase the activity of the pancreas and its proteolytic power, while in animals from which the spleen has been removed the blood of the crural vein is as active in this manner as is the blood of the gastro-epiploic vein. Splenic extracts injected into the vein produce a fall of blood-pressure, followed later by a rise, with elevation of temperature.

Landau and Hirsh have very recently obtained from spleen pulp by antiseptic autolysis a preparation termed **stagnin,** which is rich in organic iron compounds and possesses not only hematinic, but also hemostatic, powers, producing by chemical action prompt coagulation of the blood. It does not cause constriction of the vessels.

Therapeutic Uses.—Theoretically, splenic extract should be administered when there is need of more lymphocytes and when there is inactivity or disease of the pancreas. In **myxedema** it has been given with apparent advantage and might be conjoined with thyroid treatment. H. C. Wood reports recovery, under its use, in a case of **exophthalmic goiter.** It has been given in **anemia** and in conditions associated with splenic enlargement. Stagnin has been used chiefly in **uterine hemorrhages,** but was also successful in **hemophilia** and will apparently be useful in checking **capillary bleeding** generally.

Administration.—Powders and tablets are made from the spleens of calves or sheep, the tentative dose being about 30 centigrams (five grains) thrice daily. **Stagnin** powder is prepared from horse-spleen, redissolved and administered by intramuscular injection, the dose being from 30 to 60 minims (2 to 4 cubic centimeters) a day.

TESTICLES

It is by no means a new suggestion that the testes furnish some internal secretion to the system. It is also well known that animals and man can live after castration and the symptoms and appearance of eunuchism are too well known to require description here. It seems probable that the nutritional consequences of castration could be more or less completely averted by feeding testicular extract. Though exceptions may occur, Anthony believes that castration before puberty is very sure to produce impotence, while castration in adult life may not immediately produce such a condition.

Diseased conditions of the testicles, whether due to their own degeneration or to disease of the spinal cord, occur with so many symptoms due to other conditions that it cannot be decided what symptoms are produced by diminished or excessive secretion of these glands.

The reports of experiments with testicular extract have been so surrounded with quackery that it is hard to sift actual results and clinical facts from suggestion and false reports.

Brown-Séquard, when he was an old man, tried injections of extract of testicles on himself, and thought that he experienced a return of vitality. In 1889 he first recommended the use of this extract for its tonic effect, especially in senility, claiming that diminution of this secretion was one of the causes of old age. He said that the extract was without effect when administered by the mouth, and consequently always used it hypodermatically; but he was careless in his antisepsis and produced many abscesses. Further experiments with this extract have not borne out his theory.

Poehl discovered an alkaloid in testicular extract to which he gave the name of **spermin.** He asserts that this is an important factor in the oxidation of tissues and suggests that it becomes inactive in the blood when the latter's alkalinity is in any way reduced.

Dixon finds that fresh testicles macerated with standard salt solution contain proteids, organic substances unaltered by boiling, and inorganic salts. Of the proteids, nucleoproteid is the most plentiful and the only one that apparently is physiologically active. After a latent period this principle causes a fall in blood-pressure due to cardiac inhibition by action on the vagus nerve.

Other experimenters have shown that hypodermatic injections of testicular extract increase the strength of exercised muscles and prevent the feeling of fatigue.

Therapeutic Uses.—The use of testicular extract is still in the experimental stage. Theoretically, it would be indicated in degenerations of the testicles, or, if Brown-Séquard's theorizing is believed, it might be given for premature **senility** or for **impotence.** It probably has its best use in **nervous debility** as an organic, phosphorus-bearing preparation. Whether the feeding of testicular extract increases the muscular power or muscular endurance, as suggested by the experiments cited, is still unproved.

Locomotor ataxia has been treated with this extract with some apparent success, perhaps because it acts as a spinal stimulant.

Administration.—Testicular extract is best prepared from the testes of young bulls or rams, and is offered in powder, tablets and solutions.

There are two kinds of spermin found in the testicles, and a spermin is also obtained from the brain and spinal cord. The dose is indefinite.

The d'Arsonval preparation is a liquid, sterilized with carbon dioxid under pressure and then filtered. The **hypodermatic dose** of this preparation is from one to four cubic centimeters.

OVARIES

Physiology.—Just what relationship a possible ovarian internal secretion bears to the economy is not known, but it must be closely related to the action of the testicular secretion. Removal of the ovaries precipitates the menopause and gives the same vasomotor disturbances as occur in the normal climacteric; deposits of fat occur and obesity is often a consequence. The relationship of the ovarian function to that of the thyroid gland has been discussed in a former chapter; but what part the ovaries play in producing the symptoms of the menopause, and what part the thyroid, it is impossible to state.

These glands probably furnish a vasodilator substance, as the secretion not only stimulates the swelling of the mucous membranes of the uterus during ovulation, but, according to Bandler, all the mucous membranes of the body are congested, notably that of the larynx and of the nose, and perspiration is increased. After double ovariotomy Curatulo found the phosphates in the system diminished. Removal of the ovaries in the cow causes the milk to become richer in fat. It is now generally considered only good surgery in hysterectomy to leave the tubes and ovaries, or at least one ovary, intact, unless they are too much diseased.

Lukaschevitch transplanted the ovaries from one animal to another, irrespective as to whether the animal was herbivorous or carnivorous. He says the transplanted ovaries take root, are nourished, and partially perform their functions, but after a while show degenerative changes, such as atrophy; although sometimes they do well for as long as three years. While these transplanted ovaries are functionating, atrophy of the generative organs and obesity are prevented and the general condition of the animal remains good. Dudley has successfully implanted healthy portions of ovaries into the uterine wall after removal of diseased tubes, thus causing a continuance of the menstrual function and preventing menopause symptoms. Nicholson sums up his review of the literature of ovarian transplantation by stating that such transplantation is possible, that pregnancy will follow in a small proportion of cases, and that there is without doubt an internal secretion of the

ovaries, which is important for the development of the genitalia and for their preservation. All of which tends to show that a healthy ovary, or at least a portion of an ovary if healthful, should be left to the patient in necessary operations.

Troitsky draws attention to the fact that mumps frequently affects the ovaries, and reports that out of thirty-three little patients with this disease thirteen had ovarian tenderness. He thinks it is possible that mumps may be responsible for some of the pathologic changes observed in the ovaries later in life.

Therapeutic Uses.—Ovarian feeding is certainly indicated after double ovariotomy, and seems to do more good at this **artificial menopause** than at the normal climacteric. Ovarian extracts should be tried for irregular **vasomotor disturbances** in women, such as hot flashes, rigors, pallor, and sweating, and may be of benefit in neurotic cases with disordered pelvic functions. Bestion has had good results from ovarian extract feeding in the disturbances of the **menopause,** and also in **amenorrhea due to chlorosis.** He gives large doses for a prolonged period—from one to two months. I believe that for this latter condition thyroid extract is much better. Ovarian substance has been used with some success in **hysteria** and in **senile debility** in women. It has also had some apparent success as an **aphrodisiac.**

Oöphorectomy for therapeutic purposes may be mentioned as a contrast to ovarian feeding. Its performance for cancer of the breast is a subject that is causing considerable discussion. It certainly should be tried only when local operative interference is impossible. Power believes that removal of the ovaries in cases of cancer of the breast is of more value before the menopause than after it.

Holländer notes three cases and reports a fourth in which **osteomalacia** in nulliparæ was cured by removal of the ovaries.

Administration.—Ovarian preparations are obtained from the cow or the sow and are offered in dry powder or tablet form, the **dose** being from 20 to 30 centigrams (three to five grains) two or three times a day.

There is also an extract called **oöphorin.**

MAMMARY GLANDS

Bell of Glasgow was probably the first to recommend and use mammary extract in cases of impaired or perverted uterine function. He believes that the administration of mammary extract tends to correct hypertrophy and flabbiness of the uterine muscle and checks the growth of fibroids or even causes such tumors to diminish in size.

Therapeutic Uses.—Shober also says that **uterine fibroids** diminish in size under treatment with mammary extract. **Menorrhagia** and **metrorrhagia** and all their attendant symptoms disappear and the uterus contracts. Crouse has noted good results in cases of uterine fibroid, hemorrhage from the uterus and dysmenorrhea. I have seen some good results from mammary treatment in **profuse menstruation of young girls** and in the **menorrhagia of subinvolution and of the menopause.** The general health also seems to improve, for the extract appears to act as a tonic.

Administration.—Mammary extracts are prepared from the mammary glands of the ewe and cow and are offered in powder and tablets. The **dose** is 20 to 30 centigrams (three to five grains) in tablets, powders, or capsules three times a day. For metrorrhagia ("uterine flowing") the **dose** should be from one to two grams (15 to 30 grains).

PAROTID GLANDS

Whether or not the parotid gland furnishes an internal secretion separate from its salivary product is not known; but the fact of its relationship to the testicles and ovaries, as shown by metastasis in mumps, caused Bell of Glasgow, in 1896, to recommend and use extracts of this gland in the treatment of ovarian neuralgias and inflammations. He says that the results of such treatment were satisfactory.

Shober tried the same treatment in ovarian disturbances, but stated that the results were not convincing. Mallet, however, reports that ovarian pain and inflammation and dysmenorrhea are not only helped but cured by parotid gland treatment. He does not suggest or advise this treatment when there is pus or any condition in which conservative surgery necessitates operative interference; but he believes that parotid gland extract **relieves the pain of dysmenorrhea** more than any other uterine sedative. He says that it ameliorates the pain referred to the back and ovaries, causes menstruation to become more regular and normal in amount, improves the general condition, and even causes pelvic exudates to undergo absorption more rapidly under local treatment than when parotid feeding is not employed. He also noted that after removal of the ovaries the flashes of heat and cold and other vasomotor disturbances are made worse by feeding with parotid extract.

Though any treatment of these conditions is so surrounded by psychic suggestion that it is difficult to be sure of one's conclusions, the enthusiasm of these reporters should cause a more extended trial of parotid gland extract in ovarian disturbances.

Administration.—Parotid gland extracts are prepared from young sheep, calves, and pigs, and are offered in powder and tablets. The **dose** is 20 centigrams (three grains) two or three times a day. During parotid treatment for pelvic disturbances the advantages derived from local applications should not be neglected.

PROSTATE GLAND

The prostate has received a small share of the interest given to the internal secretions. Orlipski believes that the prostate furnishes a spermin as an internal secretion, and this is a tonic to the system. He therefore recommends massage of the prostate in neurasthenia. Prostate gland preparations have also been recommended for spermatorrhea and for enlargements of the prostate. It is still undecided whether any positive results can be obtained by this treatment.

Preparations are made from the prostate gland of the bull as a dry powder and in tablet form.

NUCLEIN

Nuclein was first brought to therapeutic notice in 1894 by Vaughan and McClintock, who proved that nuclein obtained from the thyroid gland, testicles, spleen and other animal tissues, but perhaps best from pure cultures of yeast, exerts a germicidal action on many bacteria.

Physiology.—Chittenden says that the term nuclein was originally applied to peculiar phosphorized substances, first isolated from the nuclei of pus-cells, and found widely distributed through nature in both the animal and the vegetable kingdom, wherever nucleated cells occur. Kossel discovered phosphorus in these nucleins, and his discoveries led to the separation of two distinct groups: those which with sulphuric acid yield nuclein bases—**true nucleins**—and those which do not yield such crystalline decomposition products—**false nucleins** or **paranucleins.** A nuclein, according to Chittenden, is simply a combination of some form of proteid with nucleic acid. **Nucleic acid** is an amorphous white powder of strong acid reaction, readily soluble in water, containing a small amount of alkali, and insoluble in alcohol and ether; it contains a large percentage of phosphorus, as much as nine per cent. being found in some forms of this acid. Nuclein readily absorbs coloring agents and the nucleins of the various cells may be identified under the microscope by this property. Mendel, Underhill and White have recently studied the nucleic acid of the wheat embryo as the only one thus far obtained from higher orders of plants, although, as above stated, the nucleic acid de-

rived from yeast has been known for some time. These investigators find that this vegetable nucleic acid resembles in its physiologic effects the guanylic acid of the pancreas. When this nucleic acid is introduced into the circulation, it produces a fall of arterial pressure and, in man, an increased output of uric acid.

Nuclein has been found to be a stimulant to all animal cells. Whether given by the mouth or hypodermatically, nuclein causes a marked leukocytosis within a few hours, varying in degree according to conditions, and principally affecting the polynuclear cells, which have been shown to be active phagocytes (Metchnikoff). The bactericidal power of blood serum is perhaps due to the nuclein secreted by the leukocytes.

Therapeutic Uses.—Feeding with nuclein increases any tendency to hemorrhage and profuse or hastened menstruation may occur as well as epistaxis. If a high degree of polymorphonuclear leukocytosis is present, as occurs in leukemia, nuclein treatment is **counterindicated.** On the other hand, if in **acute infections,** protective leukocytosis is not sufficiently pronounced, nuclein or some preparation containing nuclein is of considerable value; but it should not be forgotten that it may cause a fall in blood-pressure. Nuclein seems to be indicated in such bacterial diseases as **diphtheria, scarlet fever, pneumonia** and **septicemia,** and perhaps is of benefit in all diseases of bacterial origin, whether local or general in their manifestations. Nuclein has been strongly recommended in **tuberculosis,** and with a streptococcus infection causing hectic fever it would seem good treatment to increase the fighting power of the leukocytes. However, in the presence of cachexia and chronic infection a leukocytosis of any considerable amount may do more harm than good to the economy, and a hyperleukocytosis would certainly be objectionable.

The value of nuclein as a carrier of physiologic **phosphorus** should perhaps cause it to be utilized in cases of **nervous debility,** depression and degenerations.

As nucleins take a large part in the production of **uric acid,** substances containing considerable quantities of nucleic acid would be counterindicated in all lithemic or gouty conditions, and ought, therefore, to be avoided when action of the kidneys is impaired.

Administration.—Various preparations are offered under the names of nuclein, protonuclein, nuclein standard, phospho-albumin, etc., some of which contain phosphorus and some of which do not. Theoretically, phosphorus-containing preparations would seem to be the most valuable. The **dose** of nuclein is from five to ten centigrams (about one to two grains) three times a day.

Antiseptic liquid preparations of nuclein are offered and may, if desired, be used **hypodermatically.** The thymus gland is rich in nuclein, as is also the yolk of egg.

BREWERS' YEAST

Brewers' yeast has long been used in domestic medicine, but its systematic study is of more recent origin. Yeast is a fungus of low plant life having the power of absorbing oxygen and giving off carbon dioxid, and of converting glucose into alcohol by the process of fermentation. The yeast used in medicine is the *Saccharomyces cerevisiæ.* As pointed out by Vaughan and McClintock, brewers' yeast is rich in nuclein and therefore has the physiologic action of nucleinic acid, including the production of leukocytosis. Yeast has other actions of its own, notably that of preventing glycosuria when large amounts of glucose which ordinarily would cause a glycosuria have been ingested.

Therapeutic Uses.—Tournier says that yeast is capable of devouring microörganisms in the same way as the phagocytes, and Doyen thinks that the action of yeast in combating **staphylococcous infection** is as specific as is antitoxin in **diphtheria.** I have administered brewers' yeast in several cases of **pelvic cellulitis** and believe that the treatment is sufficiently effective to warrant its further trial. Ullman states that brewers' yeast was used for **furunculosis** as far back as 1852, and many clinicians now recommend this yeast in the treatment of local pustular inflammations, as boils, carbuncles, acne and folliculitis. Petri recommends yeast for **suppurative skin diseases,** as impetigo contagiosa, and states that he has hastened the cure of confluent small-pox by giving teaspoonful doses three times a day. Other observers, however, have seen no results from this treatment in small-pox. Vandamme finds that brewers' yeast obviates the necessity of depriving **diabetics** of bread and carbohydrates. Roos recommends the use of yeast in obstinate **constipation.** Yeast is also of advantage in the treatment of **urticaria,** doubtless on account of its ability to modify fermentative processes in the intestine. Albert uses yeast as a vaginal injection in all cases of **leukorrhea,** and believes that it acts as a cleanser and germicide by its phagocytic powers. Yeast can be applied with advantage to suppurating wounds and eroded cancers. Ullman urges the use of brewers' yeast in cases of **tuberculosis** when there are secondary infections and profuse bronchial catarrh.

Administration.—Brewers' yeast is best employed fresh and in liquid form. Two kinds of yeast occur in the manufacture of beer, called the "high" and the "low," and pure cultures do not allow the trans-

formation of one of these varieties into the other. Yeast contains *invertin, alcoholase*, and other unknown enzymes. The **dose** of fresh yeast is from a teaspoonful to a tablespoonful three to five times a day in milk or water.

When fresh yeast cannot be obtained, a dried product called **cerevisine** may be used. Cerevisine is a granulated, dry form of yeast, soluble in water, and may be given in solution or in wafers. The **dose** is a teaspoonful three or four times a day. For use in the vagina one or two grams (15 to 30 grains) may be made into a suppository, or the yeast may be inserted into the vagina as a glycerin paste. Cerevisine is less liable to cause fermentation and eructations of gas from the stomach than liquid yeast, but its phagocytic powers are probably less active.

LECITHIN

Lecithin, from the Greek λέκιθος, meaning yolk, is found in the yolk of egg, in nerve tissue, in leukocytes and in the semen. It contains a good deal of organic phosphorus, to which it probably owes its therapeutic value. Chemically, lecithin is made up of acid glycerophosphates. Bang has found that the nucleoproteid of the pancreas splits up into phosphoric acid and glycerin, forming glycerophosphoric acid; hence its constitution closely resembles that of lecithin.

Physiology.—Lecithin is a constituent of all kinds of cells and is really a fat; it breaks up into a fatty acid and a nitrogenous body, termed cholin. Cholin, which is itself harmless may, however, be converted into neurin, which is poisonous. It has not been decided whether the lecithin found in the tissues comes directly from the food or is formed in the body. Cholin is found in the intestinal canal during fermentation, especially when there is obstinate constipation or obstruction. There are several kinds of lecithin, which may be broken up into cholin and various fatty acids.

Animals fed on lecithin gain in weight over control animals; but the ingestion of large quantities of lecithin as food or medicine would certainly be objectionable, as there is a possibility of the cholin being changed in the intestine into neurin, which is toxic. Wood finds neurin, the decomposition product of cholin, to be a paralyzant of the sensory nerves, the motor nerves and the spinal centers in the order named. The pulse is slowed by injections of neurin, and death occurs from respiratory failure. Ariès has carefully examined the urine in patients taking lecithin, and finds that with an average dose of 30 centigrams (five grains) it causes an increase of urea, a diminution of uric acid and a

very marked increase of acidity. According to the researches of Desgrez and Zaky, phosphate elimination is decreased by lecithin (Lenn).

Therapeutic Uses.—Lecithin, from the investigations cited, seems to be indicated as a tissue builder in **debility** and may be given with advantage in **tuberculosis,** in **neurasthenia** and in other forms of **malnutrition.**

Lecithin should never be administered in gouty conditions, as it tends to decrease the excretion of uric acid.

Administration.—Lecithin is difficult to preserve. It is offered diluted with oil, and put up in capsules of one grain each, the **dose** being one capsule three times a day; or it may be administered as a glycerol of lecithin, sold in sealed eight-ounce bottles, the dose of which is two cubic centimeters (half a teaspoonful) three times a day, in milk or water. Elixirs containing lecithin are offered and are eligible preparations.

Several organic powders are offered, under various trade names, the active principles of which are largely *nuclein* and *lecithin.*

GLYCEROPHOSPHATES

The glycerophosphates are closely allied to lecithin. Glycerophosphoric acid is the glycerin ester of phosphoric acid; the neutral salts of this acid are most generally used, as they are stable. These neutral salts of glycerophosphoric acid are ready for assimilation and seem to improve the nutrition much as does lecithin, promoting metabolism and increasing the output of nitrogen in the form of urea, while diminishing the phosphorus loss. During their administration the excretion of uric acid diminishes, possibly because more nitrogen goes into urea formation. Weber states that elimination of sodium chlorid is increased, and thinks that this is the cause of the improved appetite under the use of glycerophosphates.

Therapeutic Uses.—The most important use for glycerophosphates is found in **neurasthenic conditions** and in **general debility,** whether from tuberculosis or from some prolonged illness. The glycerophosphates of calcium and sodium are those most used, although for rickets Weber recommends the glycerophosphates of calcium and magnesium.

In phosphaturia and in certain forms of unexplained malnutrition the glycerophosphates will probably prove beneficial they are also indicated in degenerative diseases of the nervous system, in neuralgias and even in hysteria.

Administration.—Glycerophosphates are generally given in solution in the form of elixirs. Either sodium glycerophosphate or the sodium and calcium combination is usually preferred.

The glycerophosphates of calcium and magnesium are used for rickets, as above stated.

Calcium glycerophosphate is a dry, white, crystalline powder, of a feebly alkaline taste, soluble in a large excess of cold water, insoluble in alcohol.

Sodium glycerophosphate is so hygroscopic that it cannot be furnished in a dry form, and the same is true of potassium glycerophosphate. Each of these is offered in a seventy-five per cent. watery solution. These are the salts that are used for hypodermatic injection.

Iron glycerophosphate occurs in yellowish-green scales or as an amorphous, yellowish-white powder, very slightly soluble in water, insoluble in alcohol.

Magnesium glycerophosphate is an amorphous, yellowish-white powder, slightly soluble in cold water, insoluble in alcohol.

Lithium glycerophosphate is a white, amorphous powder, soluble in water, insoluble in alcohol.

Manganese glycerophosphate is a bright pink powder, practically insoluble.

Quinin glycerophosphate occurs as white, needle-like crystals, practically insoluble.

The **dose** of any of the powders mentioned is from 25 to 50 centigrams (about four to eight grains), best given in wafer or capsule. The potassium glycerophosphates are offered only as weak elixirs, the dose of which is five to ten cubic centimeters (one to two teaspoonfuls). Many of the elixirs are combined with iron.

Most of the preparations cited may be obtained in tablet form or in sealed capsules.

MUSCLE TISSUE (Zomotherapy)

Muscle extract contains potassium salts in considerable quantity and, if given hypodermatically, might, therefore, be toxic; but by the mouth it is a tonic to the muscular system and as such has been recommended for various muscle degenerations. Myosin albumin represents a large amount of nutriment and is readily digested in the stomach and quickly absorbed.

Raw beef, or the expressed serum from uncooked beef, has been recommended in **tuberculosis.** Possibly the beginning of such treatment dates back fifty or more years, when tuberculous patients were sent to the slaughter-houses to drink the fresh, warm blood of slaughtered cattle. Richet and Héricourt were, perhaps, the first to experiment scientifically with meat juice or ζωμός (broth) in tuberculosis. They

reported striking results, stating that the feeding of raw meat or fresh muscle juice to dogs with tuberculosis greatly retarded the progress of the disease, and, if the treatment was begun early enough, would arrest the disease, at least temporarily. Cooked meat had no such curative effect. They also asserted that suralimentation without raw meat was less effective than an exclusive raw meat diet, even in underfed animals, apparently showing that muscle juice possesses a specific action. Robin and Binet have determined that the respiratory exchange of carbon dioxid for oxygen is greater in pulmonary tuberculosis and in those predisposed to the disease than in healthy individuals, thus confirming an old and well-nigh forgotten observation of Beddoes.* This increased respiratory exchange was diminished by cod-liver oil and raw meat more than by any other treatment. On the other hand, Brown, presenting the results of his investigations with this treatment of tuberculosis, states that he finds no specific action from raw meat. He states, however, that as a food for tuberculous patients raw meat is better than well-cooked meat, and that in forced alimentation myosin albumin affords an easily digestible food for the extra nutrition. Rarely it may cause diarrhea. He further says that juice from raw meat is little, if at all, more beneficial than the juice from meat slightly browned, and patients often prefer the latter to the raw juice. This coincides with the editor's experience. Fränkel and Soberheim also find that muscle juice is not a specific in tuberculous animals.

Héricourt recommends the meat juice as especially beneficial during the **pretuberculous** period, and in the first and second stages of tuberculosis; the appetite increases and the nervous tone of the patient improves. During the third or cachectic stage he finds that much raw meat or muscle serum may give rise to symptoms of intoxication; perhaps because the action of the liver is impaired.

Raw beef juice is certainly of great value as a nutriment, and perhaps as an organic extract, in prolonged **acute infections** and in **chronic debility.**

Administration.—Héricourt directs that fresh, lean, raw, chopped steak be macerated for two hours in one-fifth part by weight of cold boiled or filtered water, after which the muscle serum is to be extracted with a meat press.

Dosage.—During the latency or first stage of pulmonary tuberculosis he recommends the juice of from 500 to 1000 grams of beef daily; during

* Cited by S. Solis Cohen, article "Tuberculosis," Hare's "System of Practical Therapeutics," 1891, first edition, vol. i, p. 813.

the second stage of the disease he administers the juice of from 1000 to 2000 grams of meat; and in the third stage of pulmonary tuberculosis and in miliary tuberculosis he gives the juice of from 2000 to 3000 grams of meat. Muscle juice as thus obtained must be taken immediately or changes rapidly take place. Hence it is sometimes best to prepare the juice twice a day. If desired, this juice may be administered with a little salt, or given in carbonated water; it should be taken an half hour before eating. If raw beef is not repugnant to the patient and is taken in sufficient quantity, it is probably as efficient as the expressed serum. The editor has used raw beef in feeding tuberculous patients for more than twenty years and with much satisfaction. His patients have fortunately escaped the only danger—tape-worm. Raw mutton does not seem to be as valuable as raw beef in these cases. The treatment should be continued for six months at least after the disappearance of all symptoms and renewed whenever there are signs of returning debility.

As raw beef juice requires so much care in its preparation, a meat powder called **zomol** has been offered, which is fresh meat juice filtered under pressure and then evaporated to a powder. Zomol may be given whenever fresh meat juice is indicated, and administered as a dry powder spread on bread with butter or stirred into a cold broth. If unpalatable to the patient, it may be given by rectal injections. The daily dose should be ten grams (two and one-half drams), which represents the soluble constituents of 200 grams of fresh meat. It must never be given in hot solutions. Zomol is offered in bottles containing 60 grams.

Musculine is an extract of the muscle tissue of the ox.

Myogen is an albumin prepared from the blood serum of freshly killed cattle, and is offered in the form of a powder and in small cakes. The latter, more agreeable to the taste and more concentrated, contain about 20 per cent. of albumin, 50 per cent. of carbohydrates and 10 per cent. of fat. Myogen is readily assimilated and nearly as nutritious as fresh meat.

RED BONE-MARROW

Physiologists are now agreed that under ordinary conditions the red bone-marrow is the source of the red blood-corpuscles. It is quite probable, although perhaps not incontrovertibly proved, that the polymorphonuclear leukocytes also have their origin in the red bone-marrow. Hence, if the bone-marrow is degenerated or diseased, there is a diminution of the red and the large white cells.

Red bone-marrow preparations contain **iron** in physiologic combi-

nation, and probably represent one of the best methods of administering iron to the system. Extracts from this bone-marrow undoubtedly stimulate the production of red blood-corpuscles, as can be demonstrated in cases of simple anemia by weekly blood counts during its administration.

Red bone-marrow preparations are indicated in **chlorosis, anemia, tuberculosis** and **general debility,** and perhaps whenever the polymorphonuclear leukocytes are diminished in number. They are typically indicated when the red marrow is diseased, as in **leukemia.**

The treatment is probably of value in **rickets** and **bone diseases** and in the **neuralgias** due to malnutrition.

Administration.—The bones of young animals contain more active marrow than those of adult animals, therefore these preparations are made from the younger bone-marrow, or red bone-marrow as it is called, and are generally offered in the form of glycerin extracts. The anterior extremities of the ribs are the bones most used in making these preparations. The **dose** of the glycerin extract is from five to ten cubic centimeters (one to two teaspoonfuls) after each meal, well diluted with water, milk or wine, to suit the patient's taste.

GASTRIC JUICE

Although it is not the province of the section on organotherapy to discuss the digestive preparations, from the standpoint of an organic extract the administration of fresh gastric juice for medicinal purposes must be mentioned.

Several experimenters, notably Pawlow of St. Petersburg, have ascertained that fresh gastric juice obtained from dogs has some therapeutic value. Finkelstein has successfully treated 22 cases of gastric affections with fresh canine gastric juice. In two cases of **gastric cancer** the pain and vomiting were lessened, the eructations of gas were diminished, and the appetite was increased. In eight cases of **gastric catarrh** all symptoms of indigestion disappeared, and cases of **diminished gastric motility** were also improved. Others clinicians have obtained equally good results. The doses of gastric juice given were from 50 to 200 cubic centimeters (about one and one-half to six ounces), administered during or after meals.

It is obvious that before gastric juice can be generally adopted as a therapeutic agent some means must be devised to preserve the product and place it on the market in a permanent form.

DUODENUM (Secretin)

An active internal secretion or extract has been obtained from the duodenum by macerating with four-tenths of one per cent. of hydrochloric acid the mucous membrane of the duodenum or jejunum of a fasting mammal. This preparation is called **secretin,** a name proposed by Bayliss and Starling. Mendel says that a very small portion of this extract injected into the circulation calls forth a copious flow of pancreatic juice. Henriquez and Hallion state that secretin is a pronounced stimulant to the liver, increasing the secretion of bile. Secretin is not present as such in the intestine, but is formed from a precursor, *prosecretin*, by the action of acid. Camus finds this secretion to be elaborated by all animals—the dog, cat, rabbit, guinea-pig, pig, pigeon and frog.

The value of this substance as a stimulant to pancreatic secretion seems to be unquestioned. How valuable it will prove clinically in intestinal indigestions has not been determined; but it seems to be an important organic extract.

Eukinase is an extract obtained from the duodenal mucous membrane of the pig and appears as a yellowish powder. Hallion and Carrion recommend the use of eukinase in **acute** and **chronic affections of the intestines** and believe it to be of marked value in intestinal indigestion.

BRAIN

The growing belief that epilepsy, in which there is no organic lesion, is caused by paroxysmal intoxication of the system, has caused therapists to seek an antitoxin or something that will combat the toxemia. The possible thyroid cause of puerperal eclampsia is in line with this theory.

Poehl of St. Petersburg reports the successful use of an extract made from fresh brain substance in **epilepsy, cerebral debility, nerve degenerations** and **delirium tremens.** Tarchanoff says that brain extract has a soothing effect on the nervous system. Lion reports brilliant results with Poehl's cerebrin in epilepsy and states that there is immediate improvement in the worse forms. The dose, he says, is 60 centigrams (ten grains) a day. Kaplan, however, reports negative results after a trial of this treatment in 13 cases of epilepsy. Many of the reported successes have had the combined treatment of bromids and *opocerebrin*. Whether the combined treatment is more efficient than the bromids alone remains for further investigation to decide. Brain extracts have been used in all

neurasthenic conditions, in **paralyses,** in **insanity** and also in **locomotor ataxia;** but the results are still subject to criticism. Tikanadze reports the recovery of a case of **tetanus** after injection with an extract of the brain substance of a freshly slaughtered young pig. He injected 10 grams of the extract in 30 cubic centimeters of salt solution and repeated this injection several times.

Injections of brain extracts sometimes cause a rise of temperature and leukocytosis—in other words, a toxic reaction which is probably due to the contained cholin or neurin. The extract also seems to act as a stimulant and tonic.

Administration.—The best preparation of cerebrin is the **opocerebrin** (Greek ὀπος, juice) of Poehl. This is a two per cent. sterilized solution put up in sealed glass bulbs. Each bulb contains two cubic centimeters of the solution, which is the **dose** for one hypodermatic injection a day.

Cerebrinum is also marketed in powders and tablets, each tablet containing 10 to 30 centigrams (about two to five grains). The dose is two or three tablets a day.

LYMPH GLANDS

The lymph glands functionate actively in childhood and are easily disturbed by every infection; leukocytosis also is more marked in a child with an infectious disease than in an adult. The enlargement of the lymph glands probably protects the body against the progress of an infection and generally subsides after the infection has been overcome. Sometimes, however, the enlargement persists, owing, probably, to continued infection or perhaps to some irritation in the neighborhood; certain children are peculiarly predisposed to such enlargement of the glands, especially those who have enlarged tonsils and adenoid growths.

Flexner has experimented on guinea-pigs with lymphotoxins and myelotoxins, and finds a reaction in the bone-marrow to lymphotoxins and in the lymph glands and spleen to bone-marrow toxins. In lymphatic leukemia there is an increased lymphocytosis, and although these lymphocytes are doubtless formed in the lymph glands, it is impossible to diminish this glandular activity.

The relationship between the spleen and the lymph glands is so intimate that theoretically the indications for **lymph gland extract** and spleen extract are the same.

Lymph-gland juice might be administered in localized infections when the neighboring lymph glands are inadequate to the task of arresting and, perhaps, combating the disease. Snow on this theory advises the use of lymph gland juice in **cancer.**

A preparation called **glandulin,** prepared from bronchial glands, has been recommended in pulmonary tuberculosis on the theory that the bronchial glands protect against and combat the tubercle bacilli.

A proprietary **"lymph compound"** is said to be made from goats less than a year old, and to represent the lymph from the lymph ducts and glands, the testicular fluid from the testicles, and extracts of the lymph glands, the spinal cord, the medulla and the gray matter of the cerebrum and cerebellum. To this, it is stated, is added testicular fluid from bulls, the whole being then diluted with goat's blood serum and distilled carbonized water and sterilized. If made as stated, it should be rich in albumin, nucleins, lecithin and phosphorus, and hence is supposed to be a general cell tonic. It is said to dilate the peripheral blood-vessels, and theoretically might be a tonic to nerve tissue and leukocytosis. It is recommended for **general debility, malnutrition, nervous** and **cerebral diseases,** and especially for **pulmonary tuberculosis.** No scientific investigation of this treatment has, however, been recorded, and the clinical reports are too laudatory to be convincing. It is mentioned merely as a matter of current medical history.

KIDNEYS

Though a patient may cease to secrete urine for several days or secrete a greatly insufficient amount, convulsive symptoms may not appear. At other times convulsions appear as soon as the kidneys cease to secrete or even before they have stopped secreting. There must, therefore, be some difference in the kidney action in the two cases, and this difference may be associated with an internal secretion (Bitzou). This theory is borne out by the fact that animals whose kidneys have been removed soon die; but if kidney extract is injected into the veins, life can be prolonged for some days. Kidney extract has for these reasons been employed with some success in uremic conditions.

Guelinel has relieved **uremic symptoms** by injecting serum obtained from the renal vein of the goat; headache and vomiting ceased, nervous disturbances were diminished, anasarca disappeared and the secretion of urine was increased.

LIVER

As illustrative of the empiric use of liver extracts, a practice not yet established on a firm basis either of physiologic experimentation or of clinical observation, I may quote a very recent report. In a case of cirrhosis of the liver in which tapping had twelve times been necessary

and in which an attack of influenza had greatly weakened the patient, Crequy administered, in conjunction with a modified milk diet and the use of potassium nitrate, one gram (15 grains) of hepatic extract daily. Hemorrhages ceased, edema and ascites disappeared. The patient was finally able to resume his occupation after having been confined to bed for eighteen months.

MUCOUS MEMBRANES (Mucin)

Whether or not we are justified in considering this tissue at all under organotherapy is an open question.

Overend describes a condition which he calls myxasthenia, or an overdryness of the mucous membranes, and discusses the relation of this condition to gout and diabetes.

A preparation from the mucous glands, called **mucin,** has been offered to combat this condition of dryness of the mucous membranes, and Stewart-Low finds mucin of value in **dry catarrh of the upper air-passages** and in certain **disturbances of the stomach.** He says that an indication for mucin is a clean, dry, perhaps fissured tongue. He finds mucin of value in **gastric ulcerations,** and states that it is a laxative.

In dry catarrhs of the nose and throat he applies mucin locally and finds that it moistens the surfaces, softens the crusts, and stops the fetor. For these purposes he uses as a spray or douche 30 centigrams (five grains) of mucin, 30 centigrams (five grains) of sodium bicarbonate, and five centigrams (about one grain) of menthol dissolved in 30 cubic centimeters (one ounce) of water.

TRUNECEK'S SERUM

For completeness of reference an attempt to imitate by art certain normal chemical juices of the body may here be mentioned.

Trunecek of Prague devised the following combination of salts for the treatment of **arteriosclerosis,** and administers it by **hypodermatic injection.** His formula, which he terms an 'artificial serum,' is:

Sodium chlorid,	4.92 grams	(75 grains)
Sodium sulphate,	0.44 gram	(7 grains)
Sodium carbonate,	0.21 "	(3 grains)
Potassium sulphate,	0.40 "	(6 grains)
Distilled water, enough to make	100 cubic centimeters	(3⅓ fluidounces).

Léopold Lévy found that he obtained as good results by oral as by subcutaneous administration. He substituted the following formula for **internal medication:**

Sodium chlorid,	75	centigrams, say	11 grains.
Sodium sulphate,	7	"	1 grain.
Sodium carbonate,	3	"	½ "
Sodium phosphate,	2	"	⅓ "
Calcium phosphate,	5	"	1 "
Magnesium phosphate,	5	"	1 "

One powder, wrapped in a wafer, three times a day.

The theory is that this combination of salts introduces into the circulation something that will dissolve the calcium phosphate deposited in the walls of the hardened vessels. Trunecek finds that all disagreeable symptoms due to high blood-pressure disappear under this treatment, and that the heart muscle is strengthened.

Gordon finds that the blood-pressure is lowered under this treatment, and he therefore recommends it in cerebral circulatory disturbances as well as in arteriosclerosis. The good results are not seen until nearly a week after treatment is begun.

Trunecek in a later article says that this serum is indicated whenever there is high arterial pulse tension without nephritis, in dyspnea, cyanosis, angina pectoris, symptoms of arteriosclerosis of the brain, and in chronic alcoholic intoxication. He states that permanent improvement takes place after from eight to ten injections, of three to five cubic centimeters each, repeated at intervals of from two to five days. By the time 100 to 150 cubic centimeters have been injected the patient is usually, he says, completely cured—a statement open to doubt.

This treatment is apparently harmless, and may be tried in arteriosclerosis, perhaps best in conjunction with potassium or sodium iodid. However, I believe that the thyroid treatment will also be found of value in the above conditions. The editor finds Trunecek's salts rarely useful in arteriosclerosis, but occasionally of good service as a diuretic.

TRANSFUSION

When this term was first introduced into medicine and surgery it meant the transfusion of **blood** from one individual to another, and in that sense the procedure belongs to the section on organotherapy. Although we have learned that the injection of standard saline solution into the veins (see Volume IX) will do all that is required of transfusion, it may not be amiss to give a brief description of this treatment, which a few years ago seemed to promise so much.

The transfusion of blood was known to the ancients, but it seems to have been a mere tradition; at least there are no recorded successes until Kaufmann and Purmann, in 1655, injected lamb's blood into a leper, and the Englishman Lower ten years later practised this treatment with some success. From that period to the early part of the last century there are occasional reports of transfusion having been resorted to, and in 1825, in England, Blondell performed some experiments on dogs. Even at this time the dangers of injecting blood from the lower animals into man were generally recognized.

In succeeding years considerable discussion took place as to whether or not the blood should be **defibrinated,** and various methods were suggested for the purpose of removing the fibrin, of which whipping the fresh blood with a glass rod is, perhaps, the best. But owing to the difficulty of removing all the fibrin quickly during the whipping process, the contamination of the blood with various aërial germs, and the fact that a large number of red corpuscles are lost by being caught in the meshes of the fibrinous mass, some surgeons preferred to inject the blood undefibrinated.

Howe recommends adding to the drawn blood two ounces of a two per cent. solution of ammonium carbonate (ten grains to the ounce) before injecting it. He believed that this prevented the formation of coagula in the veins, and was also a stimulant to the patient. The method did not win general favor.

Two forms only of transfusion of blood should be considered, the **immediate** and the **mediate.** Peritoneal injections and the injection of blood into the deep cellular tissue I believe to be unjustifiable. **Immediate transfusion** consists in transferring the blood directly from the donor to the patient by means of simple connecting tubes. In **mediate transfusion,** the method that is generally adopted, the blood is drawn into a receptacle and later injected into the patient. It seems best to abstract blood for transfusion not only from a healthy individual, but from one who is not nervous. The blood is drawn, as in ordinary venesection, from the median basilic or the median cephalic vein at the elbow, and the cannula used should not be too small, so as to minimize the danger of coagulation. The blood is drawn into a glass or china receptacle which rests in warm water. If it is decided to **defibrinate,** the blood is now whipped with a glass rod and strained through a piece of muslin into another bowl, which also rests in water at the temperature of 110° F. (43.3° C.). The blood is then ready for use and is injected slowly, best into the median cephalic vein of the patient, by means of a warmed glass funnel and tube which can be raised or lowered, according to the

pressure desired, or to which is attached a syringe. The Dieulafoy aspirator can be used for transfusion. Asepsis must be preserved.

Whatever be the cause for which transfusion of blood is undertaken, several unpleasant symptoms may occur during its progress. These are principally dizziness, a feeling of constriction of the chest with dyspnea, pain in the lumbar region, perhaps stupor and even coma. The appearance of any of these unpleasant symptoms should cause a cessation of the transfusion, at least until the symptoms have abated.

As has been stated, the transfusion should be slow, and the quantity injected, governed by the symptoms, should be from two to four ounces. The subsequent symptoms are a slight rise in temperature, often preceded by a chill, with perhaps headache, backache, thirst and some changes in the urinary excretion.

Indications for transfusion of blood are primarily, of course, **excessive hemorrhage** and the withdrawal of considerable blood containing useless red corpuscles, as after **poisoning by carbon monoxid.** Secondarily, transfusion of blood has been recommended and used for profound **anemias, purpura hæmorrhagica, scurvy, carcinoma** and **malignant syphilis,** some success having been reported in each of these conditions.

The danger of the treatment itself is the possible formation of coagula and the entrance of too much air into the veins, both of which can undoubtedly be obviated by proper instruments and good technic. However, the difficulties of the technic and the necessity of obtaining a suitable donor, coupled with the fact that the results of this treatment for excessive hemorrhage and to dilute toxins in the blood are no better than when saline solutions are injected, have caused transfusion to be practically abandoned at the present day.

Bier has recently reported some success in transfusing lamb's blood into tuberculous patients; but it is doubtful if many clinicians will follow this method.

The **transfusion of milk** requires but a word. This measure began its history in 1850, in Toronto, and was practised somewhat in this country in subsequent years. But it was found that its use both in man and in animals was almost always followed by death. Consequently, the transfusion of milk, whether from the cow or goat, is now probably never done, and I believe its injection either into a vein or into the peritoneal cavity is unjustifiable.

Venefusion of **saline solutions,** which has entirely superseded the transfusion of blood, is described in the article on Saline Infusions in Volume IX of this system.

RADIUM, THORIUM AND RADIOACTIVITY

BY

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RADIUM, THORIUM AND RADIOACTIVITY

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Evolution of Radiology

In order to have a correct conception of radium and of some of its properties it is necessary to consider the discovery and action of certain other physical agencies which step by step led to this discovery.

Geissler's Tubes.—In the middle of the nineteenth century Geissler of Bonn discovered that when an electric discharge took place in a vacuum tube, the spark, instead of pursuing a zigzag linear path for a distance limited to a few inches, was able to traverse several feet, breaking up into a diffused light that lit up the entire tube, the color of the luminescence depending on the gas or gases contained in the tube. Tubes constructed for the exhibition of these phenomena are known as "Geissler's tubes."

Cathode Rays.—In 1879 Sir William Crookes of London made an elaborate investigation of vacuum tubes, and succeeded in producing tubes with a much higher vacuum than had ever been attained by Geissler. The exhaustion of a Crookes' tube is about one one-thousandth part of that of a Geissler's tube, or one one-millionth of an atmosphere. Crookes found that in passing a current through these tubes a luminosity was produced on the side of the tube exactly opposite to the cathode, or negative pole. The cause of this luminosity was shown to be the impact against the walls of the tube of material particles traveling with an enormous velocity. The path followed by these particles constituted the "Crookes rays" or "cathode rays." J. J. Thomson estimated these particles as being in size only one one-thousandth part of the mass of an atom of hydrogen.

Roentgen Rays.—In 1898, when Professor Roentgen of Wurzburg was experimenting with a Crookes' tube of high vacuum, he noticed that the rays therefrom, falling on a screen of barium platinocyanid that was lying near by, excited fluorescence in the screen. He further

noticed that even when he stood between the tube and the screen but little obstruction to the induction of fluorescence took place, thus showing that the rays penetrated his body. Following up the idea thus set in motion, he tried the effect of interposing various substances between the tube and the screen, from which he established the fact that the penetrating power of the rays varied according to the nature of the substance interposed and with the mass of that substance. He next tried the effect of the rays on a photographic plate, and found that they acted upon it in a manner similar to that of light. The interposition of various solid substances, such as the hand, by protecting the sensitized surface in a degree corresponding to the varying densities of the parts interposed, produced a shadow-picture when the plate was developed. Thus was discovered the Roentgen ray, or *x*-ray, and its practical application, the radiogram.

Becquerel Rays.—The following year, 1896, Becquerel of Paris, when investigating the properties of the Roentgen ray, particularly the excitation of fluorescence and its effects on the photographic plate, recalled the fact that salts of uranium became fluorescent under the action of the sun's rays. To see what effect this fluorescence would have on the sensitized plate he shielded a plate against light by enveloping it in non-actinic paper, and placed on the non-actinic covering some **uranium potassium sulphate**; he then exposed the whole to the rays of the sun, thinking that the fluorescence aroused in the salt by the sun would perhaps penetrate the covering of the plate and act upon it chemically. As he expected, this proved to be the case. He then prepared to take a picture of a key by laying it on the shielded plate and covering it with the salt, but as some days passed without sunshine, he could not expose it. He developed the plate, however, and found that an excellent picture had been produced, thus proving that the action on the plate was due to properties inherent in the salt itself and not to its absorption of the sun's rays. From this came the discovery of the "Becquerel rays," a property of radiation found to be possessed by minerals other than uranium.

Radium.—In the same year Madame Curie of Paris repeated Becquerel's experiments, not only with uranium, but also with pitchblende, the ore from which uranium is obtained. She found that a specimen of pitchblende gave better pictures than could be accounted for by its uranium content, from which the inference was obvious that the ore must contain other substances more "radioactive" than uranium itself. After two years of the most painstaking research, in which she was assisted by her husband, Professor Curie of the Ecole Polytechnique,

she discovered two new elements: the first, polonium, was not much more radioactive than uranium, but the second was the marvelous substance, **radium,** the properties of which are now exciting the attention of the entire civilized world.

THE PHYSICOCHEMISTRY OF RADIUM

Pure metallic radium has not yet been isolated; but that is of small moment, for, as Professor Curie points out, like sodium, it would be very unstable and would at once be destroyed by oxidation. The chlorid and bromid are, however, permanent salts. Radium is an element of the alkaline group, having its place between barium and thorium. It is obtained from pitchblende, a comparatively rare ore. Up to the present time pitchblende has been found in rare quantities in Bohemia, Saxony; Caldwell, England, and Colorado and Texas in the United States. Over a hundred years ago Klaproth, a German chemist, separated uranium from pitchblende, and its salts have been used in medicine and the arts ever since. Radium is obtained from the refuse of pitchblende after the uranium has been extracted. Chemically pure radium salts are now manufactured by the Société Centrale of Paris at $1000 a grain or $9,000,000 a pound. The German preparation manufactured in Hamburg, at the laboratory of Dr. Richard Sthamer, is just as active and not quite so expensive.

Mode of Production.—In brief, the radium salt is obtained by crushing the residue from pitchblende, or uraninite, after the extraction of the uranium; lead, silicon and aluminum are dissolved out by boiling with sodium hydrate, washing, and treating with hydrochloric acid. The residue is boiled with concentrated sodium carbonate. The precipitated carbonates are dissolved in pure hydrochloric acid, and the barium and radium, together with calcium, lead and iron, are then precipitated with sulphuric acid as sulphates and converted into insoluble carbonates by boiling with concentrated sodium carbonate. These carbonates are then dissolved in hydrochloric acid, the lead precipitated with hydrogen sulphid and the filtrate treated with sodium carbonate. The barium, calcium and radium carbonates thus formed are freed from the calcium by washing with pure hydrochloric acid, which also converts the barium and radium into chlorids. About eight kilograms of barium and radium chlorids are obtained from 1000 kilograms of pitchblende residue. The **radioactivity** of the material thus produced is about 60, taking that of uranium as the unit. By a series of resolutions and recrystallizations, termed "fractionation," continued until the spectrum shows a com-

parative freedom from barium lines, the radium salt (chlorid) is obtained in increasing purity and radioactivity.

Physical Characters

The salt, when pure, consists of colorless crystals, which may be crushed into a grayish-white powder resembling common salt. In an impure state it has a yellowish or pinkish tinge. Its atomic weight, as determined by chemical methods by Madame Curie, is 225; but Professor W. N. Hartley estimates it, by means of spark spectra, at 257.8. Madame Curie's estimate, however, is the one generally accepted at present. Demarquay has shown the spark spectrum of radium to have fifteen lines peculiar to itself and no line belonging to any other element.

Physical Properties

Radium possesses remarkable properties in relation to the following physical phenomena: temperature, electrochemics, luminescence and radiation.

Temperature.—Professor Curie has found by experiment that radium maintains its own temperature of from 2° to 3° F. above that of the surrounding air. This observation has been confirmed by Laborde and others, and is equivalent to stating that radium gives off sufficient heat to melt its own weight of ice every hour. This evolution of heat goes on constantly, without any obvious source of renewal, for an indefinite period, leaving the radium as potent at the end of several months' use as it was at the beginning. Even after prolonged use no perceptible change, microscopic, spectroscopic, chemical or functional, can be detected. Its very weight, so far as the most delicate balance can determine, practically remains unaltered. Radium, even when immersed in the extreme cold of liquid hydrogen, instead of becoming cooler, emits more heat and light. These statements have been verified by Becquerel and Curie of Paris, Sir William Crookes and Lord Kelvin of England, Rutherford and Soddy of Canada and others.

Electrochemics.—If the radium salt be dissolved in water, a portion of the water will be decomposed into its constituent gases. Moreover, radium induces a chemical change in glass, as is shown by a change in color, to a violet or blackish tinge, of the glass tube containing it. It ozonizes oxygen and reduces silver salt, iron peroxid and potassium chromate in the presence of organic substances. Rock-salt turns blue under the influence of radium.

Madame Curie states that the glass receptacle in which radium is kept is charged spontaneously with electricity. Moreover, if the terminals

of a coil are set somewhat farther apart than sparking distance, and a tube containing radium is held near, the spark will be found to pass when a discharge is made, showing that the intervening air has been converted into a conductor. If the ordinary gold-leaf electroscope is charged with electricity so that the leaves diverge, the approach of a tube containing radium will result in the instantaneous discharge of the electricity and the leaves will fall together again. Should a glass vessel containing radium have a weak spot,—a flaw in the glass or a deep scratch, for instance,—the vessel is apt to break up like an overcharged Leyden jar.

Luminescence.—Radium bromid and chlorid, when freshly prepared and dry, possess the property of self-luminescence. A moist atmosphere, however, prevents or dissipates the luminescence, as also does prolonged heating at 1000 degrees F. or keeping the radium salt in a vacuum. Ernest Merritt of Cornell states, however, that when radium is put in a vacuum, it still continues to emit the Becquerel rays as strongly as ever.

Radium also possesses the power of communicating luminosity to such fluorescent substances as willemite (a zinc silicate from Franklin, N. J.), quinin sulphate, salicin, salol, sodium chlorid and others to be mentioned later.

A decigram of radium will illuminate a square decimeter of surface sufficiently to enable print or writing to be read.

Radiation.—The three properties of radium thus far described, together with others to which the remainder of this paper will be devoted, are dependent upon **radioactivity**—the constant emission by radium (and other substances) of Becquerel rays. (See page 126.)

What, then, is the nature of these rays? By many they have been held to be undulatory in character, like light-waves. It is, however, now generally conceded that at least some of them—and those the most effective—consist of a stream of actual material particles, termed "emanations" by Rutherford, "corpuscles" (from a supposed analogy to the corpuscles of the Newtonian emission theory of light) by Thomson and radions by the editor of this series. The existence of these material particles has been demonstrated both by Professor and by Madame Curie. In her original thesis Madame Curie showed that an emanation, and not mere radiant energy, caused radioactivity. In a closed box a flask containing radium was affixed to a thick leaden screen, and in the receptacle were placed, in varying relation to the radium flask, a series of plates. When the flask was stoppered, none of the plates underwent any modification; but when it was unstoppered, all the plates became radioactive, those between which and the radium the screen was inter-

posed equally with the rest. The radiations can pass through glass and if they were the cause of radioactivity, the plates should have become radioactive when the flask was stoppered; while the plate protected by the lead screen should not have been so affected, even when the stopper was removed.

Again, Madame Curie showed an apparatus consisting of two glass bulbs connected by a tube in such a manner that the air can be exhausted from one bulb and the connecting tube, exhaustion of the other bulb being prevented by a stop-cock. The exhausted tube contains zinc sulphid, a substance which glows with a brilliant blue-white light under the influence of radium. The other bulb, shut off from exhaustion by a stop-cock, contains a solution of radium. As soon as the stop-cock is turned the emanations, which cannot pass through glass, ascend the tube, and, reaching the zinc sulphid in the other bulb, cause it to glow. Had the rays been the radioactive factor, since they can penetrate glass, the shutting-off of their container by the stop-cock would not have prevented them from stimulating the luminescence of the zinc sulphid.

My own experience with radioactivity differs somewhat from that of Madame Curie, the results of my experiments tending to show that induced radioactivity is produced by the radiation from pure radium bromid. For example, a hermetically sealed tube containing twenty-five milligrams of pure radium bromid was placed in a liter of distilled water, to which had been added seven grams of sodium chlorid. The tube containing the radium was suspended in this solution for twenty-four hours. The radium was then removed and the solution tested. Radioactivity was found to be present. It must be concluded that the radioactive properties that were imparted to this solution came through the glass of the tube, and if, as is generally admitted, the emanations do not penetrate glass, it is only reasonable to suppose that the induced activity in the solution was due to the radiations.

Becquerel rays differ in other respects from light-rays inasmuch as they are neither reflected nor refracted in passing through media of varying densities. Thus, they cannot be brought to a focus by a lens, and they produce on the sensitized plate only shadow-pictures, like those of the Roentgen rays, to which, however, they are markedly inferior.

Henry Crookes has invented an instrument called a **spinthariscope,** to demonstrate the emanations from radium. It is, in effect, a fluorescent screen of Sidot's blende, over which moves a point resembling the second-hand of a watch, and coated with a small quantity of radium. By means of a good lens the scintillations of light caused by the impact

of the emanations on the screen may be seen to resemble a meteoric display of shooting stars.

Radium emanations possess all the properties of a heavy gas. Sir William Ramsay has shown that they can be collected in minute flasks, weighed, measured and used for a time to demonstrate the properties of the substance. By degrees, however, comes a change, and after a time the contents of the flask *cease to give the spectrum of radium*, which is displaced with more and more glowing brilliancy by that of **helium.**

The **source** of the heat and other radiant energy of radium is at present a mystery. Curie speculates upon two hypotheses : (1) As the atoms of radium are evolved they are transformed, and this transformation produces heat. (2) It is possible that radium is capable of capturing and utilizing some radiations of an unknown nature, which cross space without our knowledge.

Against this latter view must be set the experiments of Rutherford, undertaken to determine whether the radioactivity of radium depended on its concentration, as was suggested by J. J. Thomson. Into one of two bulbs connected by a cross tube was placed a milligram of pure solid radium bromid, and into the other a solution of radium chlorid. The radioactivity of each having been determined separately, the apparatus was tilted so as to permit the passage of the radium solution into the other tube, dissolving the radium bromid. No appreciable change in the radioactivity was observable after a month's interval. From this it would appear that the dissemination of the radiant matter through a greatly increased volume does not affect the radioactivity and that the activity is probably not derived from the absorption of an external radiation.

Sir William Ramsay expresses his view thus: "Those elements with high atomic weight, such as thorium, uranium and radium, are apparently decomposing into elements with low atomic weight; in doing so they give off heat and also possess the curious property of radioactivity. What these elements are is unknown, except in one case: one of the products of the decomposition of the emanation from radium is helium."

Rutherford says: "It is supposed that a certain small fraction of the atoms of the radioactive elements are at any moment unstable, and that each unstable atom throws off from itself an alpha particle. The system left behind, which is changed in chemical properties, is again unstable and projects another alpha particle, and this process continues through five or six well-marked changes. On this view the emanation from radium consists of the radium atom minus one or

more alpha particles. The matter which produces excited activity is in turn derived from the expulsion of an alpha particle from the particle of the emanation. On this view the energy given out by radium is derived from the atom itself. The energy is latent in the atom and is released during the processes of successive disintegration." From these considerations Rutherford concludes that since the emanation is unstable, it cannot consist of any known kind of matter, though the alpha particle, the final product of change, may so consist. With Soddy, therefore, he thinks that helium, which is an invariable companion of radioactive elements, is a product of their transformation. Ramsay and Soddy have found that helium is produced in minute quantity by the radium emanation, whence it is probable that helium is in reality the alpha particle that is projected with such velocity from radium. In other words, we are actually witnessing the slow spontaneous transformation of matter. It has recently been suggested that radium is itself a transformation product of uranium. The basis of this opinion is the variation in the ratio of uranium and radium richness in certain specimens of pitchblende—the uranium content apparently diminishing as the radium increases.

The rays have been divided by Crookes into three kinds, which he has termed respectively **alpha, beta** and **gamma rays.** Of these, the first two are certainly emanations. From a comparison of the various descriptions of these rays by Crookes, Rutherford and Madame Curie we are enabled to formulate the following tabular description:

Alpha.	Beta.	Gamma.
1. Due to flight of material particles the size of atoms of hydrogen or helium.	1. Due to flight of material particles—electrons, $\frac{1}{1000}$ part of the mass of a hydrogen atom (Rutherford), matter in the fourth, or ultragaseous, state (Crookes).	1. Not material.
2. Electrically positive.	2. Electrically negative.	2.
3. Most numerous.	3.	3. Least numerous.
4. Behave like projectiles.	4. Ditto, but more forcibly than alpha.	4. Do not behave like projectiles.
5. Velocity, 20,000 miles a second.	5. Velocity, 1,000,000 miles a second.	5. Velocity enormous.
6. Comparatively easily absorbed by material obstructions.	6. Not so easily absorbed by material obstructions as alpha.	6. Not easily absorbed.
7. Penetration much less than beta. Will not penetrate an aluminum plate more than $\frac{5}{10000}$ of a centimeter thick.	7. Penetration much greater than alpha. Will penetrate an aluminum plate $\frac{5}{100}$ of a centimeter thick.	7. Extraordinarily penetrating. Will penetrate an aluminum plate 8 centimeters thick.
8. Slightly deflected in the magnetic field.	8. Readily deflected in the magnetic field.	8. Not deflected in the magnetic field.

Alpha.	Beta.	Gamma.
9. No analogues.	9. Analogous to or identical with cathode rays (Crookes, Rutherford).	9. Analogous to (identical with, Crookes) Roentgen rays.
10. Render air a conductor of electricity, giving off positive particles.	10. Render air a conductor of electricity, giving off negative particles.	10.
11. Act on a photographic plate.	11. Act on photographic plate.	11. Act on photographic plate.
12. Act strongly on Sidot's blende, but feebly on barium platinocyanid.	12. Act strongly on barium platinocyanid, feebly on Sidot's blende.	12. Act strongly on barium platinocyanid, feebly on Sidot's blende.
13. Excite luminescent substances.	13. Excite luminescent substances.	13. Excite luminescent substances.

Definition of Radioactivity

The following definition of radioactivity was suggested by K. W. Millican and amended by Rutherford.

The radioactivity of a substance may be defined as the property possessed by it of continuously and spontaneously expelling from itself, with enormous velocity, charged particles of matter capable of passing through the interspaces of other atomic matter, and of producing kinetic, thermal, electric and chemical phenomena in contiguous or adjacent atoms without *appreciable* change in the chemical or spectroscopic characteristics or the molecular or atomic alliances of the radiant substance itself.

The property of radioactivity is not confined to radium. It is known to be shared by uranium and thorium, by the new element polonium, discovered by Madame Curie in pitchblende, and by actinium, another supposed new element, found in the same source as the others, by M. A. Debierne in 1898. More will be said on this subject hereafter. It is considered probable that most, if not all, things possess radioactivity in some degree not at present appreciable. For instance, C. T. R. Wilson has shown radioactivity to be present in freshly fallen rain-water and snow.

The relation between radioactivity and **electricity** is suggested by the experiments of Elster and Geitel, who have shown that certain metallic substances when suspended in midair and strongly charged with negative electricity, become radioactive. These investigators have taken radiograph pictures with scrapings from a copper rod that they had treated in this way. Moreover, the earth being the great reservoir of negative electricity, the pointed extremities of lightning conductors, leaf spines of trees and the like, are in a state of negative electric tension, and Thomson has shown them to be radioactive also.

The Detection of Radioactivity

The presence of radioactivity in any substance may be tested by—

(*a*) The electroscope; (*b*) the sensitized plate; (*c*) its capacity for ionizing the air.

(*a*) When a radioactive substance is brought near the wire attached to the two gold leaves in the **electroscope,** the leaves fall together, indicating the discharge of the electricity. The greater the rate of the discharging power of the leaves, the greater the radioactivity.

(*b*) If a **photographic plate** be protected from the action of light by a nonactinic covering, it is acted upon by the proximity of any radioactive substance, and the silver salts are reduced, just as though the plate had been exposed in the ordinary way to light. Moreover, if

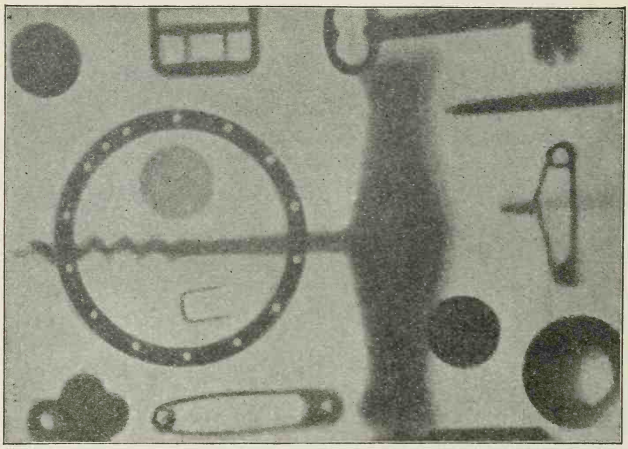

FIG. 11.—RADIOGRAM TAKEN WITH ONE-SIXTH OF A GRAIN OF RADIUM BROMID OF 1,000,000 RADIOACTIVITY. Photographic plate placed inside of black paper cover. Distance of radium from plate, four inches. Time of exposure, ten hours.

some object opposing more or less resistance to the passage of the radiations be interposed between the radioactive substance and the plate, a **shadow-picture** (skiagram) will be produced. Such objects may be a portion of the human body, a key or other metallic substance, or what not. (See Figs. 11, 12.)

(*c*) G. B. Pegram of New York considers the electric method of testing radioactivity the most accurate. On the lower of two parallel plates the radioactive substance is spread out in a thin layer. The electric conductivity—*i. e.*, the **ionization of the air** between the plates—

is measured by the current that can be sent from one to the other. This is accurately obtained by the rate of deflection of the needle in the quadrant electrometer.

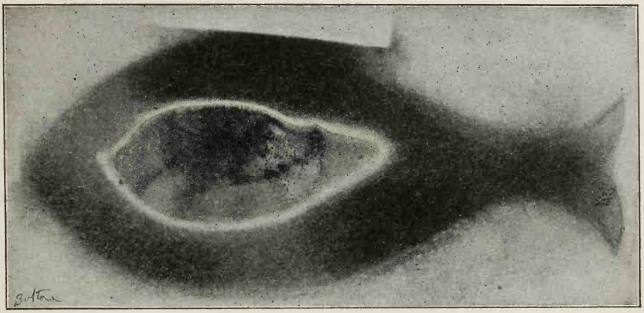

FIG. 12.—RADIOGRAM OF A PERCH. The fish was placed upon a photographic plate, which was enveloped in black paper. On top of the fish rested one tube of radium of 15,000 radioactivity. Another tube of radium (1,000,000 radioactivity) was suspended four inches above it. Time of exposure, eighteen hours.

FIG. 13.—RADIOGRAM OF A BRASS EAGLE. Taken with two-fifths of a grain of radium bromid. Radioactivity, 1,000,000. Plate exposed directly to the radium. Time of exposure, three minutes.

Measurement of Radioactivity.—The effects produced by a given quantity of uranium are taken as the standard unit of radioactivity.

The radioactivity of other substances, as polonium, thorium and radium, is gaged by comparison of their effects with those of the same quantity of uranium under the same conditions. The highest radioactivity at present known is said to be 1,800,000.

A rough measure is found in the thickness of the iron screen that the rays will penetrate so as to render a barium platinocyanid screen fluorescent when placed behind the iron. Twenty-five milligrams of pure radium bromid of 1,000,000 activity should illuminate a fluorescent screen through one inch of soft iron, or produce a radiogram through ten inches of wood after forty-eight hours' exposure. Pure radium bromid will make a radiogram in a dark room on an uncovered plate in three minutes (see Fig. 13), and in six minutes when the plate is covered with the ordinary paper wrapping.

PHYSIOLOGIC EFFECTS OF RADIUM

The physiologic effects of radium are manifested chiefly on—(*a*) the skin; (*b*) the nervous system; and (*c*) the visual organs.

(*a*) If a small glass tube containing radium of 1,000,000 activity be carried in the vest-pocket for three hours, a **dermatitis** will set up which will not fully manifest itself for a week or ten days. If, however, the radium be carried in the pocket for ten hours, a severe burn may result. These burns will cause ulceration, which will take several weeks or even months to heal. In guinea-pigs destruction of the epidermis and dermis, with loss of hair, is produced in twenty-four hours by keeping a tube containing fifty milligrams of pure radium bromid in contact with the skin. If the tube be retained *in situ* for forty-eight hours, the wound does not penetrate deeper, showing that the muscular and other deeper tissues are not strongly affected. Curiously enough, in one rabbit subjected to the same experiment the growth of hair was stimulated.

(*b*) M. Danysz, as the result of extensive experiments on mice, guinea-pigs, rabbits, caterpillars and butterflies, finds that the **nervous system** of animals is intensely sensitive to the radium rays. The introduction of a tube containing one milligram of a radium salt of 300,000 activity beneath the skin of the back of a mouse has caused paralysis, followed by tetanic convulsions and death. That this effect was due to the radium is clear from the fact that similar mice used as controls tolerated larger tubes not containing radium without any ill consequences. In a rabbit which had been trephined the insertion of a radium tube under the dura mater for eight hours resulted in a left hemiplegia.

(*c*) Giessel has called attention to the fact that when a tube containing a radium salt is brought near the closed eyes or in immediate contact with the eyelids or the temporal region, a sensation of light is produced. This sensation of light is perceptible also by persons suffering from certain forms of blindness.

Effects on Vegetable and Lower Animal Life.—On the germinating seeds of plants the effects are varied. Experiments on garden-cress and white mustard showed no interference with germination after twenty-four hours' exposure, but after a week's exposure the seeds failed to sprout. Canary seeds exposed by Robert Abbe for forty hours to rays with a radioactivity of 300,000 sprouted and grew better than controls subjected to exactly the same conditions of light and moisture. Becquerel, on the other hand, found that various kinds of seeds lost their germinating power after exposure to the rays.

It is not absolutely essential that the radium should be in actual contact with the animal organism to produce its effects. Danysz suspended five milligrams of radium chlorid of 300,000 activity over a cage containing two parent white mice and six little ones. After three days the little mice began to lose their fur. Three days later their backs were devoid of fur, though that on their heads remained. In two days more the young ones became blind, and from that time began to die, the last one perishing twelve days after the beginning of the experiment. On the twenty-third day the parent mice became blind. On the forty-sixth day, both died. In another experiment two full-grown mice under the influence of the same quantity of radium remained well for nine days, though they appeared terrified; they died the next day without losing their fur. On the other hand, larger animals, such as rabbits, when subjected to the action of the rays for a shorter time or to rays of lesser intensity, not only did not seem to suffer, but seemed even to thrive. Herein we may see an exemplification of that principle which seems to underlie all vital action, namely, that a primary action is apparently followed by an opposite reaction. Gymnastic exercise proportioned to the powers of the subject gives tone and increased vigor; excess results in fatigue. Opium is a brain stimulant in minute doses; carried beyond a certain point it induces cerebral exhaustion. And so with most, if not all, drugs, including alcohol and tobacco. Action to a certain point gives vigor; at that point supervenes exhaustion, and functional impairment results.

Effects on Animal Development.—Bohn's experiments show that exposure to radium checks the rate of growth of toad embryos. The various stages of development of sea-urchins were checked or impaired

by it.* On the other hand, Bohn affirms that he has been able to effect, by exposure of the unfecundated eggs of the sea-urchin to the influence of radium, results similar to those obtained in Loeb's famous experiments on parthenogenesis, by modifying the saline constitution of the water. Danysz found that the larvæ of *ephestia kuebniella* were killed by being exposed in a glass tube to the action of radium, with the exception of one or two that managed to escape out of reach of the rays, where they lived on in the larval state for months; while other larvæ in a control flask during the same time became moths which laid eggs that were hatched into other larvæ, which in their turn became moths. Bohn states further that he has even produced "monsters" in tadpoles by subjecting them to the influence of radium at the transition periods of their growth. Bohn gleans from his observations that the rays affect only the growth of tissues and organisms. The greater effect on the skin, in contradistinction to the insignificant effect on the deeper tissues, muscles and serous membranes, can thus be explained, because the cuticular elements are in a constant state of renewal and development.

Bacteriologic Effects of Radioactivity.—The observations made with radium in bacteriology have been somewhat limited. Ashkassi and Caspari, however, assert that the suspension of radium directly over a culture-plate of *Micrococcus prodigiosus* inhibits the growth of the organism in two hours and has a fatal effect in three hours. The *Bacillus liquefaciens* and *Bacillus coli communis* (Henry Crookes), *Bacillus anthracis* (Danysz), *cholera bacillus* (Pfeiffer) and *typhoid bacillus* (Friedberger) are also said to be inhibited in their growth by exposure to the rays from ten milligrams of pure radium salts. Van Beuren and Zinsser † report six careful experiments in which twelve milligrams of radium of an estimated activity of 300,000 failed to show inhibiting or germicidal effects upon bacterial cultures. Their results, however, do not accord with those of other observers.

THE THERAPEUTICS OF RADIUM

From all that has preceded it is easy to infer that there are latent in radium great therapeutic possibilities. This inference is necessarily strengthened when we consider the many points of similarity between the radium rays and the *x*-rays. It is true that even this latter agent is only

* Hence also the selective tendency of the rays in regard to malignant tissues of an embryonic character.

† "Amer. Med.," Dec. 24, 1903.

on the threshold of investigation as to its therapeutic value; still, the literature on the subject amply demonstrates that enough has been established to put it on a firm basis as a therapeutic agent, leaving to careful experiment the definition of its limitations.

Limitations of Radium Therapy.—The effects of radium are exerted principally on (*a*) The cutaneous tissues; (*b*) the nervous system; (*c*) the visual apparatus. We should, therefore, naturally look in these directions for therapeutic effects, and in this the analogy of the Roentgen rays bears us out. To these must be added, as means of application can be devised, the use of radium as a bactericide. More will be said of this under **induced radioactivity.** The literature of radiotherapy is necessarily limited as yet; but a cursory review of the cases reported so far is at least encouraging. It shows that a limited number of good results have been obtained in cancer, including both epithelioma and a few cases of internal cancer, in other malignant tumors, in rodent ulcer, in lupus and in various skin diseases. The treatment in almost all cases in which it was employed was found to diminish the pain and the discharge. It is, nevertheless, needful to modify the too enthusiastic forecasts framed in the first glamour of apparent success with a marvelous remedy. We can still be hopeful, but we must admit that positive achievements have fallen short of expectation. In my own hands, after many months' faithful trial, radium has proved of little value in cases of internal cancer (sarcoma and carcinoma). Disappointment is the result generally reported as to cancers of the mouth, tongue and rectum, the precise situations where most was to be anticipated and where the first brilliant successes were achieved. It may be that to the difficulty in procuring the agent, and hence to deficiencies either in strength or in quantity, much of this disappointment is to be attributed. Neither a gram of 7000 radioactivity nor 10 milligrams of 300,000 radioactivity can be expected to accomplish what might be possible with a gram—*a fortiori* with 10 grams—of 1,000,000 radioactivity. The therapeutic powers of radium must receive further study under the most favorable conditions before final verdict can be rendered.

Cancer and Diseases of the Skin.—Personal experience may be cited to show possibilities. I have thus far treated four cases of epithelioma, three of lupus erythematosus and one of psoriasis, by exposure to radium. In one of the cases of epithelioma the growth had existed twelve years; it was situated on the neck, measuring two and one-half by one and one-half inches, and was elevated about one-quarter of an inch above the surrounding parts. A tube containing ten milligrams of radium of 500,000 radioactivity was employed in this case. Three exposures were

made weekly of fifteen to twenty minutes' duration each, with the tube held about one inch from the center of the growth. After twenty-five applications the growth was healed over for the first time in five years. In the second case the growth was scraped before the radium treatment was begun. The latter was the same as in the first case, and after eighteen exposures the part was entirely healed. The scraping appears to assist the healing process, especially in preventing the formation of elevated borders.

The case of lupus erythematosus is still under treatment. In this case I am using twenty-five milligrams of pure radium bromid, with exposures lasting half an hour. The growth is much improved, flatter, less red, and is making rapid progress toward a cure.

The case of psoriasis is one of twelve years' standing. Of the numerous spots, one on the back of the left hand was selected for radium treatment. A tube containing one grain of radium and barium, of 15,000 radioactivity, was supported about one inch above the back of the hand for a period of twenty minutes at a time twice weekly. After two weeks' treatment there was a marked improvement, indicated by a gradual fading and scaling of the spots. The patient is still under treatment.

Of course, it may be truly objected that it is idle to talk of a "cure" of any malignant disease until a sufficient number of years have elapsed to preclude the likelihood of a recurrence. On the other hand, when we compare with operative measures the comparative simplicity of radium treatment, its painlessness, its freedom from danger to life and the absence of any unpleasant features, we must frankly admit that, should healing be produced, we are no worse off than after a surgical operation, even if the growth recurs; while we have avoided all the suffering and, above all, the dread inspired by an operation, and are equally able to do so if recurrence takes place. Moreover, it must be remembered that the excision of so much tissue, including the diseased part, even if it were certain that all the diseased tissue had been removed, is not quite so reassuring as the actual retrogression of the growth itself under our very eyes. Unjustifiable delay in operation is, nevertheless, not to be permitted under delusive hopes of achieving impossible results with radium. In cases of malignant disease in which the site, the character, the rapidity of growth or other clinical or mechanical characteristics preclude the period of waiting attendant on attempts at cure by radiotherapy, operation may, however, well be supplemented by treatment with *x*-rays or radium in the endeavor to prevent recurrence. In nonoperable cases radiotherapy of some kind is our only hope. At present

their greater available quantity and greater penetration give to *x*-rays the preference in many cases; but should radium be produced more cheaply, so that the necessary quantity and power may both be used, the greater ease in handling it and the more continuous application possible, together with the facility with which it may be introduced into certain accessible cavities, will be advantages not to be despised.

Diseases of the Nervous System.—This field has not yet received the attention that it deserves. Few reports of the value of radium in nervous diseases have so far appeared in the literature, except the cases I report. Yet it is to be remarked that in many, if not in most, of the cases hitherto cited the relief from pain has been noted as a prominent effect of the radium application. Darier, moreover, calls special attention to the "analytic effect" of the radium in his case of cancer, and also in a case of ophthalmic neuralgia which had resisted all efforts at relief for over six months, as well as in cases of iridocyclitis and other painful affections.* W. W. Keen of Philadelphia also informs me that he has been using radium with excellent results for the relief of pain in cancer and obstinate neuralgia.

I myself have used it with good results in facial neuralgia, facial paralysis and in a case of **spasmodic tic,** in which the first improvement for several months was brought about by a single exposure to radium. As the patient is still under treatment, it is too early to speak of the result. The treatment consists of three exposures weekly, each of one-half hour's duration, to five milligrams of pure radium bromid applied over the facial nerve where it emerges in front of the ear. The anesthesia of the right side of the face is much relieved, and the tactile sensibility is almost normal. For a week the patient has had no convulsive movement at all in the lower right side of face; the twitching around the eye is much less frequent, but the attacks are still as severe as before treatment was begun.

Effects on the Visual System.—Diseases of the Eye.—The light-producing effects of radium suggest that in certain forms of blindness radium may perhaps find a useful sphere of action. In atrophy of the optic nerve the rays may possibly restore its activity. In forms of functional blindness, in which the retina is intact, good results may be hoped for. Radium, moreover, serves as a prognostic aid in determining whether the removal of a cataract will restore sight or not. There are but few cases of experiment in this direction on record. Lunden of Berlin affirms that by the use of radium he has obtained good results

* "Medicine," December, 1903, p. 925.

in the case of two boys who were almost totally blind. Unfortunately, the cause of the blindness is not mentioned. While these boys were not cured, Lunden found after several exposures that they were able to see shadows of objects which they had been unable to distinguish before. I have treated a number of cases of blindness, mostly cases of **optic atrophy,** in which the subjects had been visionless, or almost so, for from seven months to forty years, but I have found little improvement in cases in which the blindness exceeded five years' duration. I can conservatively say, however, that radium is worth trying in those cases of optic atrophy in which the patient can distinguish light from darkness and in which the blindness has not existed for over four or five years.

In three cases of this kind that have come under my personal observation and are in fact still under treatment the improvement, so far as determined by counting the fingers and by reading the letters on the test-card, was unmistakable after periods of treatment varying from eleven days to two months. I used radium of 500,000 activity, which was held within one-quarter of an inch to one-half an inch of the eyelid and sometimes brought into actual contact with it. The exposures lasted from two to twenty minutes and were given daily or only two or three times a week. In one case of paralysis of the optic nerve the treatment was assisted by ordering the instillation of radium fluid at home, three drops three times a day. Unfortunately, the character of the results is not clear and their permanence does not seem at all assured.

Recapitulation.—From my experience with radium, both in hospital and in private practice, I am convinced that the radiations from radium have a positive effect on diseased tissues; and, even at this early stage of experimentation it seems certain that their tentative use is indicated in **lupus** and other forms of **tuberculosis;** in **rodent ulcer, superficial cancer** and some cases of **deep cancer ;** in **chronic skin diseases ;** in **atrophy of the optic nerve** and blindness from some other causes; also in certain nerve affections, as **neuralgia, facial paralysis** and **spasmodic tic.** I have seen in some of these cases, after but a few weeks, evidence of the beneficial effect of radium. As radium rays give off electrified particles, which travel at the rate of from 20,000 to 500,000 miles a second, according as they emanate from the alpha, the beta or the gamma rays, it is only reasonable to suppose that they have a marked influence on pathologic conditions. They may be harmonious or inharmonious to the vibrations of human tissues, and particularly to the vibration in the nervous structures.

Deep-seated cancers have not, as a rule, been treated successfully by the *x*-ray. In radium rays it seems as though we may find a new agent

which, under the limitations already pointed out, is more likely to give good results in some of the cases that have heretofore been considered incurable. In treating these deep-seated affections radium rays can be applied locally, through their emanations, or by radioinduced fluids (to be referred to hereafter) directly to the seat of the disease, thus having a distinct advantage over the *x*-rays. From the cases that I have treated I feel satisfied that we are on the right road to relieve many chronic conditions formerly considered intractable. Pulmonary, laryngeal and other forms of **tuberculosis** also offer an evident field for the study, and perhaps the success, of radium treatment.

TECHNIC OF RADIOTHERAPY

Radium being virtually new to science and but of short experience as a therapeutic agent, there are many things to learn about its best mode of use: the best preparation as regards radioactive power; the length of exposure; the distance from the part; and the frequency of the applications.

The Preparation of Radium to be Used.—From my observation of the use of radium salt in medicine—and I feel quite competent to judge, having made more than 1000 personal applications—I should say, in general terms, that little is to be expected from the preparations of low radioactivity—*i. e.*, those of from 2000 to 20,000 R. From personal experience I favor the use of pure radium salts, either bromid or chlorid, which have a radioactivity of about a million. The amount used at each exposure should be not less than ten milligrams; twenty-five or fifty milligrams would be better. A grain or more is needed to affect extensive areas of diseased tissue. So low an activity as 300,000 may be used, but the exposure must then be longer. If only the low activities, say those of from 7000 to 20,000, are available, the exposure should last from twelve to forty-eight hours.

The length of exposure for pure radium bromid will depend somewhat upon the case. In optic atrophy from twenty to thirty minutes may be given every day at first, then three times a week, and the use of radium fluid at home be prescribed—three drops three times a day. For epithelioma, or skin cancer, an exposure of from twenty to forty-five minutes is necessary.

Mode of Application.—An aluminum tube or capsule as a container for radium has been suggested by Lieber. He asserts that the alpha and beta rays pass through aluminum more freely than through glass. If this be true, no doubt we should get a greater physiologic

and therapeutic action. Personally, my observations have been with a glass tube. Metallic capsules with aluminum or mica windows may be attached to holders of various shapes and thus conveniently introduced into the nose, larynx, esophagus, stomach, vagina, urethra, uterus and other localities. These have been termed *radiodes*. If the capsule be of flexible lead, it can be molded as desired.

When the **cancer** is small and there is not much discharge, the tube of radium should be placed in contact with the part. When the area is large, it is best to begin with the tube at a distance of two inches from the center of the growth and to repeat the application every day for a week or two, then three times a week. In the treatment of **cavities,** or whenever a handle is necessary, as in cancer of the mouth, I attach the radium tube to an aluminum applicator by means of adhesive plaster, winding one or two layers around one end of the tube, then binding the applicator to the plaster. This is done to prevent breaking or cracking of the tube. In cancer of cavities I apply the radium tube directly to the part for from thirty to sixty minutes every day for two weeks, then three times for a week. Exner fixed a capsule containing sixty milligrams of pure radium bromid on the end of an esophageal sound, by which means he introduced the rays into the esophagus for twenty minutes at each sitting. The stenosed part underwent dilatation. Perforation is, however, a danger to be guarded against. It is possible that a similar maneuver might be serviceable in stricture of the urethra.

Carcinoma and **sarcoma** are not easily affected by radium. These growths require a long exposure and continuous treatment. **Lupus vulgaris** and **lupus erythematosus** do not respond readily to radium. In such cases I use pure radium of 1,000,000 radioactivity. When the area of the growth is small, the radium tube is to be brought into direct contact with the part from half an hour to one hour every day, then three times a week. Cancers are more quickly and more favorably affected by first **scraping** off the crusts and producing a slightly raw surface.

In **nervous affections** I apply the tube over the nerve at its point of emergence. For instance, in the treatment of the facial nerve the tube is placed in contact with the skin, parallel with the nerve and just in front of the ear, for fifteen or twenty minutes; then it is placed over the area of pain—in this case usually above and below the eye. These parts are exposed for from ten to twenty minutes, making the whole sitting from twenty-five to forty minutes.

INDUCED RADIOACTIVITY

By induced radioactivity is meant the apparent transference, to a body not itself radioactive, of the property of radioactivity, after exposure for a greater or less time to the radiation from a self-radioactive body; such induced radioactivity not ceasing with the withdrawal of the inducing radioactive substance, but persisting for a longer or shorter period and disappearing only by degrees.

This induced radioactivity differs seemingly not at all in kind from inherent radioactivity. Its presence can be demonstrated by exactly the same methods as that of inherent radioactivity—both by the electroscope and by the photographic plate. Practically, whatever inherent radioactivity can effect, the induced form also can accomplish, though in a lesser degree. Curie noticed that after working for some time in his laboratory or handling or being much in the proximity of radium his clothing, and possibly himself, became so markedly radioactive that it was useless for him to continue his work, owing to the disturbing influence that he himself exerted on his delicate measuring instruments, which marred the accuracy of their records.

Hammer tore up a pasteboard box in which he had kept some specimens of radium, but the pieces were not destroyed. Six days later, looking at the pieces of pasteboard in the dark, he found that they were luminous, like radium itself.

When a tube of radium is wrapped in cotton in a dark room, the entire mass becomes luminous; this is due not only to the passage of the rays through the cotton, but also to the cotton itself acquiring induced radioactivity.

It will easily be seen that this property of inducing radioactivity in other substances widely extends the possible uses of radium, especially in medicine. The small quantity of radium available and its consequent prohibitive price necessarily circumscribe its use. The possibility of imparting its properties to other substances will greatly extend the sphere of usefulness of a single specimen in any community.

Radium Fluid.—As a result of extensive experiments I have found that one of the most receptive media for this induced radioactivity is the so-called physiologic salt solution—0.06 per cent. The method of induction is exceedingly simple. Into a flask containing the salt solution were placed two glass tubes, one of which contained a small quantity of pure radium bromid having the highest R known, namely, 1,000,000 plus (Professor William Hallock of Columbia University tested for me a 0.5 per cent. specimen, and found it to possess a radioactivity

of 9000. This would give 1,800,000 for 100 per cent. pure); the other tube contained ten milligrams of 500,000 R. These tubes were left in the physiologic salt solution for twenty-four hours, after which they were removed and the salt solution allowed to stand in a rack for twenty-four hours longer. It was then examined and found to be impregnated with the properties of the radium. The evidence of the induced radioactivity is found in the accompanying radiogram (Fig. 14), which was obtained as follows: In a dark room metallic substances easily recognizable in the picture were placed on a sensitized photo-

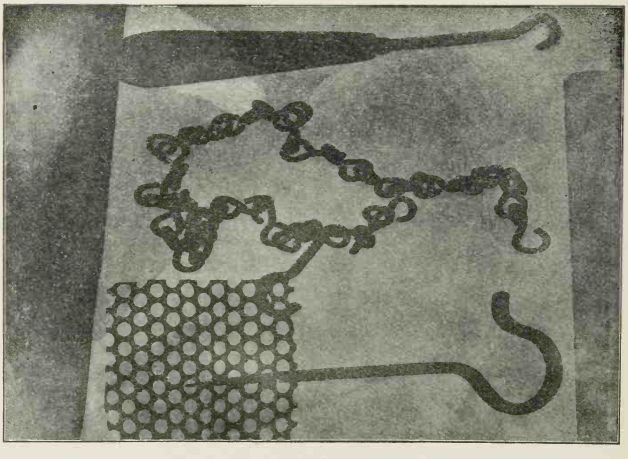

FIG. 14.—INDUCED RADIOGRAM. Taken with radium fluid. On a photographic plate rested a chain, a square of perforated brass, shoe-buttoner, etc. Over this was placed a bottle containing the radium fluid. Time of exposure, twenty-four hours.

graphic plate. Suspended above the plate was a test-tube containing half an ounce of the salt solution treated as just described, which I shall hereafter call **radium fluid.** The length of exposure was twenty-four hours. This experiment was repeated one week, and again three weeks, later, with the same solution and the same result, thus proving that at the end of even three weeks the induced radioactivity had not been dissipated.

The radioactivity of the salt solution may be stimulated by burning magnesium near it, or by exposing it to the spark from a Leyden jar

or a static machine. Exposure to the ultra-violet rays will also stimulate it.

Among other fluids that may be employed for the application of induced radioactivity may be mentioned various oils, glycerin, hydrogen dioxid and alcohol.

Modes of Employment.—The manifold uses to which radioactive salt solution can be put indicate a very wide field for its employment. It can be used externally in lotions and compresses, for dressings, gargles, collyria, sprays, nasal and other douches, hypodermatic injections, hypodermatoclysis, and even intravenously, while it can also be given internally. This makes it possible virtually to bring the action of radium into direct contact with any part of the human economy in whatever cases it may reasonably be deemed proper to investigate its effects.

Special Applications

The **antifermentative effect** of radium was shown by Hugo Lieber, who demonstrated that grape-juice, when exposed to radioactive matter, will not ferment for a month, even though it be kept in a hot room with the flask uncorked. Lieber, moreover, filled two flasks with agar and mold, such as may be taken from fermented fruit. Into one of these flasks, but not into the other, he placed a tube of radium. On exposing these flasks to the same conditions the growth of the mold was inhibited in the flask containing the radium, while in the other flask the mold grew quickly, soon filling it.

This antifermentative action is possessed, though in a lesser degree, by radium fluid. The ease, moreover, with which the fluid can be obtained, renewed, and applied to any part of the body, internal or external, more than counterbalances the loss of activity.

Further investigations are urgently called for to ascertain precisely the extent of this antifermentative action, and also to define its effect on various bacterial and animalcular infections. *Bacillus tuberculosis*, especially, should be experimented with in relation to radioactive fluids; for, should it be found that such fluids inhibit the growth of the germ under conditions favorable to its development, they can be brought into direct contact with the focus of disease.

Another morbid condition in which the induced radioactivity of salt solution is likely to prove of service is **fermentative gastro-intestinal dyspepsia,** with its long train of symptoms due to autointoxication. It may also reasonably be hoped that the drinking of the radium fluid will have a markedly favorable effect on malignant disease of the stomach and intestinal canal.

Furthermore, for home treatment, by way of local application to **skin diseases, superficial cancers,** etc., under treatment by direct subjection to rays from very powerful radium salts it will doubtless be found an invaluable adjuvant. By means of a lotion to be used in compresses or sprayed on the part, or for ophthalmic patients as a collyrium, the stimulant action of the actual rays may be reinforced with safety by the patient. This in itself is no slight advantage.

In other cases, where the radium itself cannot be used, or for some good reason it is desirable to use radium fluid, it may be introduced into the part by cataphoresis. (See Volume II.) The positive electrode is to be immersed in the radium fluid and applied to the diseased part; the negative electrode moistened with salt water, being applied to some indifferent part of the body, preferably as near to the other electrode as convenient and on the opposite side to that affected.

Radium fluid and certain natural radioactive spring waters have been injected hypodermically and into the body of a neoplasm. These methods are said by some observers to have favorable results, particularly in giving relief to pain. The introduction into the tissues of a glass tube containing radium has also been suggested, but to me this does not appear a desirable method of treating cancerous growths.

FLUORESCENCE AND RADIOFLUORESCENCE IN THERAPEUTICS

Fluorescence and Phosphorescence.—When the visible rays of the solar spectrum, between the red and the violet, fall upon any substance, they are either transmitted or absorbed. If absorbed, they are lost to view; if transmitted, either by reflection or by refraction, the rays, or rather the body upon which they fall, becomes visible.

There are, however, other rays, which have been termed rays of "invisible light." These rays proceed from either extremity of the spectrum beyond the red and the violet, those beyond the red being generally termed infra red and "heat rays," and those beyond the violet, ultra violet and "actinic rays." Proceeding from the red end of the solar spectrum toward the violet end the rays progressively become shorter in wave length and of greater velocity. Passing beyond the confines of the solar spectrum into the fields of the invisible rays, at either end, those at the red end continue to become longer and slower than the red, while those beyond the violet become progressively shorter and of greater velocity.

Now there are some bodies which, when certain of these rays beyond

the ends of the visible solar spectrum fall upon them, glow with a peculiar light: in other words, they render these invisible rays visible, as all bodies render visible those incident rays of the light spectrum that they do not absorb. This luminous appearance under the stimulus of the "invisible rays" is termed **fluorescence** or **phosphorescence.**

Much confusion occurs in the use of these terms. The custom which seems most satisfactory is that of Stokes and Levison. In 1882 W. G. Levison defined phosphorescence as the making visible of the longer rays from the ultra-red end of the spectrum, as in 1852 Stokes had said fluorescence was the making visible of the shorter rays from the ultra-violet end of the spectrum. These effects are due to the rendering shorter and quicker of the rays from the ultra-red or heat end, and the rendering longer and slower of the rays from the ultra-violet end, of the spectrum, thus bringing them within the limits of vibratory rapidity which the retina is capable of taking cognizance of in either direction.

To illustrate the phenomenon at the ultra-violet end of the spectrum Tyndall said, in 1870: "When nonvisual waves are caused to impinge on the molecules of certain substances, sulphate of quinin, for example, they compel those molecules or their constituent atoms to vibrate, and the vibrations which are set up are of a slower period than those of the exciting waves. To this change of the rays from a higher to a lower refrangibility Stokes has given the name "fluorescence."

As to the distinction between the rays from the other (the ultra-red) end of the spectrum and those described by Tyndall, Levison, in a personal letter, says: "I cannot see the propriety of calling the fluorescent after-glow phosphorescence, unless some other term is adopted for phosphorescence caused by heat; every substance that is fluorescent affords (when the exciting cause is removed) an after-glow of longer or shorter duration, and it can be reproduced just as often and as long as the active substance is exposed to the light or other exciting agency. Phosphorescence, on the contrary, is only produced once, and then soon dies out, even though the temperature is maintained. As both fluorescence and the fluorescent after-glow are produced only by wave energy of shorter wave-length than the light generated, I first, in my lectures (1898), called substances which exhibited this effect step-down transformers of radiant energy. Since phosphorescence changes the energy of the longer, invisible wave-length (as the invisible infra-red) to visible light of shorter wave-lengths, I call substances that are phosphorescent step-up transformers of radiant energy."

Fluorescence in the Human Tissues.—Natural fluorescence in the body was known as far back as 1855, when Helmholtz examined

the retina of the eye of a man who had been dead for eighteen hours and found it slightly fluorescent. In 1859 J. Setschenow of Moscow examined the retina of a living man for fluorescence, and found that the fresh retina showed the same phenomenon as Helmholtz had demonstrated in the dead eye. He noted that it diffused a greenish light, which, when examined by a prism, gave a spectrum in which the red was wanting. The fluorescence began (as in quinin solution) between the lines G and H, was strongest in the outer edge of the violet and extended into the ultra-violet.

In 1867 Bence Jones said, in his lectures on "Pathology and Therapeutics," that there seemed to be "some substance in the human body that resembled sulphate of quinia, and, circulating in the blood, caused all the tissues of the body to become more or less fluorescent." This substance he named "animal quinoidine." This phenomenon was particularly noticeable in the crystalline lens. He further found quinin to be fluorescent in the proportion of 1 part to 1,800,000, and that when sodium sulphate was added to quinin sulphate, the fluorescence was increased; when this was introduced into the body the maximum amount of fluorescence was observed at the end of three hours, remaining until the end of six hours, when it gradually disappeared.

The Relation of the Fluorescence of the Animal Tissues to Disease.—Bence Jones was also the first to suggest that the lack of natural fluorescence in the system facilitates the contracting of malarial disease; and he was the first to point out, in 1867, that the reason that quinin cured ague might be because it furnished to the system a sufficient artificial fluorescence to compensate for the loss of its natural fluorescence. Rhoads and Pepper later reaffirmed this proposition. Our recent knowledge of the malarial parasite suggests a rational explanation of this theory by supposing that that organism is incapable of thriving in a fluorescent medium. If such be the case, it is rational to suppose that the artificial induction of fluorescence in the body will prove effective in malaria, and probably in many other conditions which, now that attention has been turned in that direction, may be found to be due to, or at least to be aided by, a similar loss of the natural fluorescence of the tissues. Probably many bacterial diseases—and almost certainly any diseases that may be found to depend on protozoan parasites—will be included in this category. A. F. A. King of Washington deserves credit for having resuscitated these old-time findings and suggesting their application in the light of our present knowledge.

Artificial Fluorescence of the Human Tissues.—Since this subject of the fluorescence of the human tissues has once more come into promi-

nence, attempts have been made to combat certain forms of disease, supposed to depend on a lack of natural fluorescence, by the induction of an artificial fluorescence in the body.

As W. J. Morton of New York points out, the process of inducing artificial fluorescence involves two distinct factors—viz., (1) The safe introduction into the body of substances capable of being excited in the tissues to fluorescence; and (2) the employment of some agency, externally or internally, which shall be able to excite the fluorescence in these substances thus introduced into, or applied to, the body.

In regard to fluorescent substances, I have made an extensive series of investigations, with the following results. Many substances are fluorescible, but not all to the same excitant. Some fluoresce under sunlight, others under the dark rays, *x*-ray, Finsen ray, or radium. Others again respond to the heat rays, phosphorescing under the influence of the ultra-red rays. In speaking of fluorescence I shall confine my remarks to those substances excitable by the *x*-ray and radium, these being the methods of inducing fluorescence most readily available to the majority of physicians. Sunlight, as Morton points out, fails to excite fluorescence when passed through a red screen, such as the blood affords; consequently we may eliminate that source.

Morton has shown that under the **x-rays,** quinin bisulphate, æsculin, fluorescin and other substances are fluorescible.

My own investigations with a number of solid substances give the following results:

Fluorescent to Radium.—*Very Little.*—Potassium chlorate, zinc sulphate, magnesium sulphate, powdered alum.

Slightly.—Most glass, especially glass bottles and goblets, test-tubes, glass shades, etc., are slightly fluorescent, hence the importance of not testing for fluorescence in a glass receptacle. Powdered red uranium oxid, black uranium oxid, chinotropin, sodium bicarbonate, borax, camphor, gum acacia, potassium hypophosphite, potassium bitartrate.

Moderately.—Powdered uranium nitrate, menthol crystals, potassium citrate, powdered quinin bisulphate.

Markedly.—Powdered sodium chlorid, salol, calcium-tungstate crystals, granulated sugar, potassium iodid.

No doubt there are many other substances which are fluorescent to radium and may be found upon further investigation.

Not Fluorescent.—I have been unable to detect fluorescence to radium in the following substances, either as a powder or in crystals: Fluorescein, eosin, orcein, boric acid, bismuth subgallate, stearate of

zinc, pulverized calcined magnesium, pulverized kaolin, pulverized chalk, pulverized calamin.

Among the fluorescent substances in the foregoing list I find that powdered potassium iodid and sodium chlorid are the most fluorescent to radium in the dry powdered state. Then follows granulated sugar (much in advance of the other soluble substances); zinc sulphid, calcium tungstate, and barium platinocyanid are the most excitable after willemite (zinc silicate).

Therapeutic Applications.—It is my practice in using radium therapeutically to have the patient take, an hour or two before exposure to the rays, from five to ten grains of **quinin,** or a suitable dose of some other of the fluorescent drugs named above, preferably **salol** or **potassium iodid.** In this way there is caused to circulate through the blood a substance which is fluorescent to the excitant, radium. This fluid can then be excited, either by exposure to the radium rays or by causing the patient to drink the physiologic salt solution rendered radioactive by exposure to the radium emanations (radium fluid, as before described). Artificial fluorescence in the tissue may be produced by the internal administration of quinin bisulphate or æsculin, etc., and the external exhibition of *x*-rays or radium. The *x*-rays will produce fluorescence over a larger field than will radium. The daily use of quinin or other fluorescent drug combined with the external use of the *x*-rays will produce an artificial fluorescence (really ultra-violet light) in the diseased tissues. By this method Morton reports cures of *lupus, tuberculous glands, Hodgkin's disease* and various forms of *cancer.* The editor has seen good results from this method—whether merely temporary or not he cannot say—in two cases of *splenomedullary leukemia.*

There is no doubt that this method enhances the effects of radium treatment in most cases in which that treatment is applicable at all. In diseases such as those referred to above, which are due, at least in part, to deficiency of the natural fluorescence of the blood, it seems certain that the artificial induction fluorescence is likely to prove a valuable therapeutic measure.

OTHER RADIOACTIVE SUBSTANCES—THORIUM

As has been stated previously, there is reason to suspect that all, or at least most, substances are to some extent radioactive, though the majority are only infinitesimally so. Emanations appear to be given off even by the animal body, according to the recent investigations of M. Charpentier.

But for practical purposes, in such a review of the subject as the present, I may confine our consideration to those substances that are radioactive in a degree that is distinctly appreciable and has some possibility of being turned to account therapeutically. I have already pointed out that the principle of radioactivity was first detected in uranium. This, indeed, is taken as the unit of radioactivity. Other elements of radioactivity besides radium and uranium are polonium,

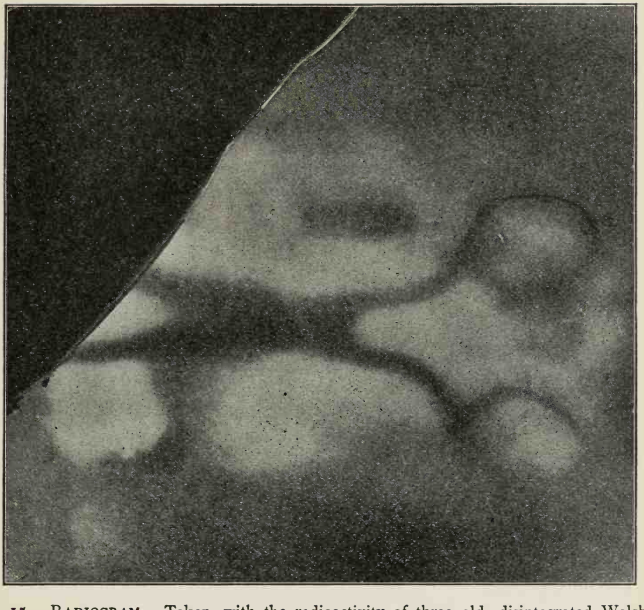

FIG. 15.—RADIOGRAM. Taken with the radioactivity of three old, disintegrated Welsbach mantles. The scissors rested on the old mantles containing the thorium oxid. Over this was placed the photographic plate. Time of exposure, seventy-two hours.

actinium and thorium. Polonium and actinium may be dismissed with a mere mention, simply stating that their properties are exactly similar to those of radium; but for various reasons they are not at present likely to be used in medicine. Thorium, however, is more important and needs a more extended notice.

Thorium is one of the rare metals and was discovered by Berzelius in 1828. Until recently it has been very rare and expensive, but during

the past ten years it has been used as the principal chemical in the production of the incandescent Welsbach mantle. It is now found more abundantly, especially in certain sands in North Carolina, in Brazil, and in Norway and Sweden. The most active thorium is obtained from the minerals cleveit, broggerit, monazite, thorite and samarskit.

The radioactivity of thorium is displayed in the usual way—viz., by discharging the electroscope and by its action on the photographic plate. Among the first thoriagrams obtained by me was the accom-

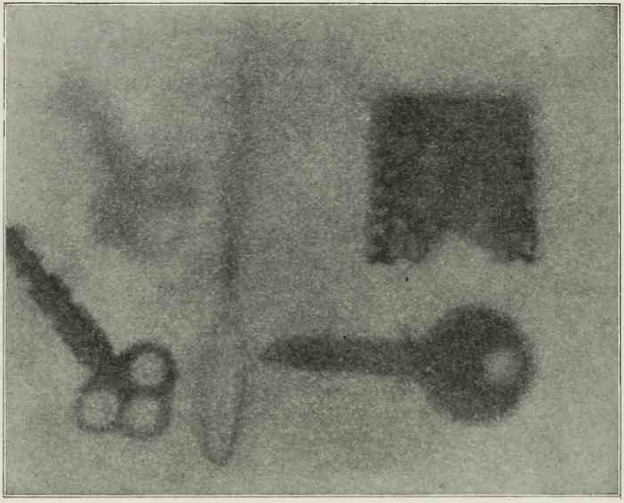

FIG. 16.—THORIAGRAM. Taken with the emanations of hot thorium oxid. Time of exposure, two hours.

panying one, taken by means of three old Welsbach mantles rich in thorium oxid. (See Figs. 15, 16.)

Rutherford and Soddy were among the first to investigate the properties of thorium. Rutherford, in 1900, found that thorium gives off an inert and highly radioactive gas, which he termed an emanation. It diffuses through gases, liquids, and even through porous substances. Rutherford considers the emanation to be the result of successive chemical changes in the thorium. The thorium atom, as a result of chemical action, produces a substance which he terms "thorium x," and by

further chemical change the thorium x produces an emanation. The emanation expels from itself a negatively charged body, which constitutes Becquerel rays, the same as those emitted by radium, polonium, actinium and uranium. The most powerful rays are obtained from hot thorium oxid.

The **antifermentative effects** of thorium have been demonstrated in a manner similar to that employed by Lieber to demonstrate those of radium—viz., by the nonfermentation of grape-juice and the nonfermentation of mold. (See page 147.)

Rutherford states that "when thorium nitrate is changed into an oxid by heat it temporarily loses its radioactivity. However, when it is exposed to the air, it soon begins to regain its activity. In four days it is one and one-half times more active; in twelve days, two and one-half times; and at the end of two weeks it reaches its maximum radioactivity, which is four times as great as was that of the original nitrate of thorium."

Therapeutic Uses of Thorium.—Thorium can, of course, be used in almost all conditions in which radium has proved of service. Its radioactivity, it is true, is many thousand times less than that of radium, but then its price also is many thousand times cheaper—viz., about twenty dollars a pound, and it can be used for a longer time at each application, so that these considerations in many cases compensate for its lack of potency.

In **chronic skin diseases,** especially those of parasitic origin, thorium oxid may be made into a twenty-five per cent. ointment and applied externally.

As an **adjunct to radium treatment,** enabling a mild degree of radioactivity to be kept up during the intervals of the radium exposures, thorium has a useful place. In my own experience I have found that in the treatment of **cancer** and other local conditions it is good practice to keep up the effect on the part by the constant application of thorium during the intervals between the exposures to radium. The thorium oxid may be placed in sealed soft-rubber or oiled-silk bags, and attached to the part with adhesive plaster.

Soddy and Rutherford have suggested the use of thorium in **tuberculosis.** The best results are likely to be obtained from the **inhalation** of the emanations. These emanations may be obtained for purposes of inhalation by breathing over a shallow receptacle containing a saturated solution of thorium nitrate. The larger the area of the vessel, the more copious are the emanations. A slight current of air can be caused to pass over the solution from a compressed-air tank while the

patient is inhaling. With the thorium nitrate there passes over more or less free nitric acid; this must be neutralized by passing the emanations before inhalation through a wash-bottle containing a saturated solution of sodium bicarbonate.

But by far the best method of inhaling thorium emanations is by means of **Hugo Lieber's inhaler.** In this apparatus thorium oxid is heated in a glass receptacle over a sand-bath. (See Fig. 17.) In using Lieber's thorium apparatus the inhalation of the emanations

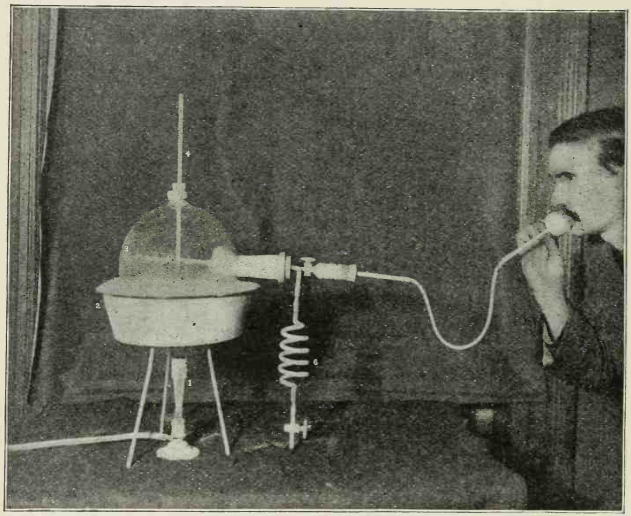

FIG. 17.—LIEBER'S APPARATUS FOR HOT THORIUM INHALATIONS. 1. Bunsen burner. 2. Tin vessel containing white sand. 3. Glass vessel containing thorium oxid. 4. Thermometer. 5. Inlet for air. 6. Spiral glass tube to prevent escape of emanations. 7. Outlet for emanations. 8. Mouthpiece for inhalations.

leaves in the pulmonary alveoli a fine film of radioactive matter, which in turn gives rise to induced radioactivity in the same parts. This induced radioactivity will remain in the air-cells long after the original emanations have been exhaled. In most cases it lasts for from one to two days, after which it gradually disappears. In this connection it is interesting to observe that the radioactivity of thorium can be proved even after it has entered the lungs. If a patient inhales the thorium emanations and then, while in a dark room, exhales, allowing the breath

to come in contact with a photographic plate, the exhalation affects, and partly decomposes, the silver salts on the plate.

The induced radioactivity of the thorium emanations lasts from twenty-four to forty-eight hours; this acts as a guide to indicate the proper frequency for the applications. An inhalation given every day or every other day would keep the lung cells constantly in a radioactive and antiseptic condition. While the thermometer in the Lieber apparatus should indicate a temperature of from 250° to 300° F., the emanations are partly cooled by passing through the glass and rubber tubing, and may not be much above the normal body-temperature at the moment of inhalation. These inhalations may be taken for a period of fifteen minutes at the outset, which may gradually be increased to half an hour.

This method of treating tuberculosis will not interfere with other measures, such as dietetic, hygienic and even drug treatment.

In closing this essay I wish to accord due credit to the various authors who have contributed to our knowledge of radium by their investigations and writings. While it is not possible to mention them all, or in an article of this character to give credit in each particular place, I would especially express my obligations to the Curies, Rutherford, Soddy, Davidson, Barker, Hallock, Pegram, Truman Abbe, Morton, Williams and several German and French authors. I also wish to thank Dr. K. W. Millican for his personal assistance in the labor of compilation.

ADDENDUM

ON

X-RAY THERAPY

X-RAY THERAPY*

The apparatus for the production of skiagrams and for the transillumination of the body by means of the Roentgen rays has been described in Volume I, Chapter V. In Volume II was given a succinct account of the performance and promise of x-ray therapy at the time that volume was printed. Short as is the time since then, the subject has made such rapid progress that it seems advisable to give a brief review of recent advances in the physics of radiation and in the practical applications of roentgenism in medicine.

PHYSICS

Roentgen's discoveries, followed quickly by those of Becquerel and Curie and the researches of Larmor, Thomson and Rutherford, have stimulated anew the spirit of investigation into the fundamental problems of natural philosophy; precipitating the long-impending change in accepted hypotheses concerning the constitution of matter and the mechanism of energy. While it cannot be said that science is yet ready to assert the identity of matter and energy, a long distance toward that position has been travelled since the days of Dalton, Helmholtz, Mayer and Joule. Not about the atom and the molecule, but about the ion and the electron, do current discussions revolve; and physicians must take notice of the change and all that it portends. This is not the place to discuss the whole subject even in outline,—far less to speculate on future developments,—but it seems advisable to point out as briefly as possible the bearing on the physics of x-ray therapy of some of the salient features of the day's most advanced theory of matter.

Sir William Crookes's "radiant state of matter" is no longer a speculation: it has been demonstrated. In the demonstration other weighty facts have come into view and promising hypotheses have been put forth. Sir Oliver Lodge has recently said: "Electricity is not a form of energy, any more than water is a form of energy. Water may be a vehicle of energy when at a high level or in motion; so may electricity. Electricity cannot be manufactured, as heat can, it can only be moved

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* For valuable aid in compiling data for this article the editor is indebted to his nephew, Dr. Myer Solis-Cohen, Assistant Visiting Physician to the Philadelphia General Hospital.

from place to place, like water; and its energy must be in the form of motion or of strain. Electricity under strain constitutes 'charge'; electricity in locomotion constitutes a current and magnetism; electricity in vibration constitutes light. What electricity itself is we do not know, but it may perhaps be a form or aspect of matter. So have taught for thirty years the disciples of Clerk Maxwell. Now we go one step further and say, Matter is composed of electricity, and of nothing else."

Upon this daring hypothesis, positive electricity represents most of the bulk (extension, position in space) of matter, while negative electricity, with little bulk (about one one-hundred-thousandth of the diameter of an atom), gives to matter more than $\frac{99}{100}$ of its mass, so that in what follows we assume "atomic weight" as an exclusive property of negative electricity. Every atom of matter may be conceived of as an atmosphere of positive electricity in which innumerable particles of negative electricity (or charge), sometimes called electrons or corpuscles,* move in different orbits. Each electron has a definite charge of electricity and this charge is found to be the same as that conveyed by each single atom when a current is passed through a chemically conducting liquid (electrolyte). Every electron has a definite and uniform mass which has been found to be about $\frac{1}{800}$ of that of an atom of hydrogen. From every kind of material the same and no other kind of electron can be obtained; hence it is asserted that no other kind exists. The differences in the properties of the atoms, by which we have hitherto differentiated the chemical elements, depend upon the differing numbers of electrons held within the elementary atoms. Hydrogen apparently contains about 800 electrons. If we represent the number 800 by n, the atomic weight of an element multiplied by n will give, approximately, the number of electrons it contains. Thus oxygen would contain about 16 n, or 12,800 electrons: mercury, 200 n, or 160,000 electrons. Radium, if we take Madame Curie's estimate of its atomic weight, contains 225 n, or 180,000 electrons.†

Within the hydrogen atom the electrons are so widely separated in proportion to their bulk that they can revolve in their orbits without collision—they have, indeed, says Lodge, a greater proportional free space than have the planets of our solar system. When, however, the number of electrons in an atom begins to exceed 200 n, although

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* The editor has suggested the terms *radions* and *ultims*.

† Taking the atomic weight of radium at about 250, and n at 1000, according to another calculation we have 250,000 electrons in the radium atom (p. 128).

there is still much free space they become relatively crowded; collisions occur; the atom breaks up and streams of electrons are ejected—in other words, the substance is radio-active. "Even in atoms of which the parts are sparsely distributed," says Lodge, "such occurrences are not impossible, though they are less frequent, and accordingly it is to be expected that every kind of matter may be radio-active to a very small extent: a probability which is now justified for most metals by direct experiment with very sensitive means of detection." According to Ramsay, exposure to radium will excite this condition in nearly all substances.

The radiation from most of the radio-active substances when analysed by the magnetic field is found to be separable into three parts: First, β rays, which are the electrons projected out from their atomic orbits—the meteorites of minute space. Second, γ rays, which appear to represent an ethereal pulse and have been compared to the sound waves set up in the air by an explosion—in this case the firing-out of the electron from the atom. Third, α rays, which are newly formed atoms of a substance different from the original atom.* These generate heat when they are stopped by any obstacle; thus in the case of radium the vessel in which it is enclosed is kept at a temperature of a degree or two higher than surrounding objects. According to Lodge, if but a single atom out of ten thousand breaks up and flings away a portion of itself once a year, that would be sufficient to account even for the exceptionally active manifestations of radium.

β rays, being negatively charged, and α rays, being positively charged, are deflected in opposite directions by the magnet; while γ rays (or ethereal pulses) are not bent at all.

The β rays (or flying electrons) are identical with the Crookes rays. The α rays, as we have seen, are new-formed atoms. As set forth in Volume I and on pages 132 and 133 of this volume, *x-rays* are considered to be ethereal pulses set up through the sudden stoppage, by the anti-cathode target, of the stream of flying electrons emitted by the charged terminal (cathode) of a vacuum tube. They are analogous to, if not identical with, the γ rays spoken of in the foregoing paragraphs.

METHODS OF TREATMENT

Current.—The *primary current* must not be too strong, 20 to 100 volts and $1\frac{1}{2}$ to 3 ampères usually sufficing. Many operators express a preference for storage batteries. Others use street-currents. *Coils* whose

* In the case of radium, this new substance is helium (see p. 131).

maximum spark-length capacity is 30 centimeters (12 inches) are preferred by many.

Tube Boxes.—Some operators prefer to enclose the tube in a box, permitting the rays to issue only in a desired direction. Thus Rollins painted many coats of white lead on the inside of a box with a sliding cover and made a circular opening in its side five centimeters in diameter, over which he fitted a circular diaphragm. The diaphragm may be of wood coated with white lead or of heavy sheet lead covered with plate glass. It has three round apertures of different sizes, any one of which can be brought opposite the opening in the box. An iris diaphragm covering the opening is even better. Circular openings 5 or 10 centimeters in diameter should be made in the top, front and back of the box and covered with pieces of plate glass 15 millimeters thick, to enable the operator to observe the tube and the area treated. After the tube has been arranged so that the rays will fall on the diseased part, the opening next the patient is covered with an aluminum screen, 0.25 millimeter thick, which then is grounded to carry off the electricity about the tube.

Protective Coverings.—The impact of the rays is limited by means of protective coverings, opaque to the rays, so applied to the body that only the diseased part is exposed. For this purpose, according to convenience and depending on the region under exposure, a metal sheet, a shield or a mask may be employed. The metal sheet should be 1 or 2 millimeters thick and should have an opening corresponding in size and shape to the area to be treated. It is merely laid upon the part. The shield is made of cardboard, or, preferably, blotting-paper, and is covered with four thicknesses of tinfoil fastened with adhesive plaster. It should extend at least 5 centimeters in every direction beyond the diseased tract, a hole being cut in it corresponding in size to the part treated. The shield is held in place by means of a bandage. The tinfoil must not come in contact with the skin and the blotting-paper should not be allowed to become moist. For the face, a mask is used, made of gauze or paper and either covered with tinfoil or painted with white lead, except at the part covering the diseased area, in which part a single opening or several small openings may be made. The mask may be held in place by means of a bandage or of an elastic band with spring clips at each end.

Technic of Exposures.—The patient should be placed in a comfortable position before the treatment is begun. The time and frequency of the exposures and the distance of the tube from the patient must be determined for each individual, each disease and each apparatus. Only general directions can be given here.

For treating **superficial growths** the tube should be placed at a distance of 15 *or* 20 *centimeters* (6 or 8 inches) from the part; in **skin diseases** the distance should be greater.

The *duration* of the exposure should be *five minutes* for the first few sittings, increased later to *ten minutes* and in the larger growths to *fifteen* or even *twenty minutes*. There should be *two* or *three sittings* a week.

SPECIAL THERAPEUTICS

Diseases of the Skin

Acne.—The x-ray has been used with success in both *acne rosacea* and *acne vulgaris*. The tube should be at a distance of 20 centimeters (8 inches). Ordinarily there should be two, or at most three, exposures weekly, each of 10 minutes' duration. When the pustules or comedones are thickly clustered, the area exposed should be large enough to include several of them, but when they are isolated, should be but slightly larger than the given lesion. Time and patience are necessary. The comedones may fall off after several exposures. In one case reported, improvement was not noticed until a few months after the discontinuance of a course of thirty-three exposures extending over three months. Atrophy of the affected glands and follicles can be produced, with consequent benefit, when small areas are affected. When the acne is more widely distributed, a permanent cure by this method would necessitate a general atrophy of the sebaceous glands of the face, the effect of which on the skin ten to twenty years later cannot be known at present. Hence caution and discrimination must be exercised in the selection of cases and in the vigor and duration of treatment.

Alopecia Areata.—The exposures should be for ten or fifteen minutes with the tube at a distance of 20 centimeters (8 inches). Several cases have been reported in which a cure has resulted after five or six exposures, but many cases have been failures. The x-rays, however, bring about quicker results than treatment by drugs in cases that would improve spontaneously or under the use of other therapeutic measures.

Baldness.—Five-minute exposures may be given, twice weekly, with the tube at a distance of 20 centimeters. A few cures have been reported, in one case after but six exposures. The treatment is attended with risk, owing to the difficulty, at present, of so adjusting the strength of the application as to stimulate the growth of hair on bare spots, without causing it to fall out from areas still covered.

Blastomycosis (Cutaneous).—Two cases have been reported in which

the borders that had not healed under treatment by potassium iodid disappeared after twelve and sixteen exposures, respectively.

Carcinoma.—See under *New Growths.*

Eczema.—The x-ray is of benefit in all forms of eczema, acute and chronic, moist and dry. Exposures of five minutes' duration may be made every second day (in some cases every day) with the anode of the tube at a distance of 15 or 20 centimeters. In acute cases relief from the painful symptoms sometimes takes place within a few hours after exposure and in most of the severe cases within a few days; but healing of the skin may require some weeks. Ointments, especially of zinc oxid, which is opaque to the rays, should not be used during the treatment. Lesions may reappear, but usually in parts that have not been exposed to the radiation.

Elephantiasis.—Favorable results have been reported. The treatment must be long continued, begun cautiously, and regulated in duration, frequency and strength according to the reaction observed.

Erythema Intertrigo.—Good results have been reported.

Favus.—Freund and Schiff used a Ruhmkorff coil with a spark-length of 30 centimeters, excited by means of six storage cells (12 volts), the resistance of the tube never exceeding 10 to 15 centimeters. Complete epilation of the scalp is essential. To expose the whole scalp the tube should be placed first over the middle of the frontal region, next opposite the sides of the head (with the anticathode opposite the middle point of a line between the ear and vertex), and finally opposite the center of the occiput. The tube should be placed at some distance (25 to 30 centimeters—10 to 12 inches), so that as large a surface as possible may be irradiated, and each exposure should be of from six to ten minutes. Before commencing operations the hair should be cut to about the length of 2 centimeters. The hair loosens after about three weeks and falls out in a circular patch within the next two weeks. After about eight days more the scalp presents a smooth, shining appearance, about six or eight weeks after the termination of irradiation becomes covered with lanugo, and later fully recovers the hair. In many cases the scalp remains permanently cured especially if a relapse does not show itself within ten weeks.

Furunculosis.—Irradiation pushed to the stage of epilation relieved for a considerable time a case of chronic furunculosis of the neck. Milder measures suffice in less obstinate cases.

Herpes Zoster.—In two cases Williams obtained temporary relief following one and two exposures respectively.

Hypertrichosis.—A course of 17 to 25 sittings should be given,

followed, after intervals of four to six weeks, by a supplementary course of 3 to 5 short daily sittings, which must be kept up for twelve to eighteen months. Freund employs a 30 centimeter coil excited by currents of two or three ampères and 110 volts. He prefers a tube distance of about 15 centimeters. A large number of cures have been reported.

Keloids.—Cases have been reported in which keloids have been removed by intermittent treatment with the x-rays during periods of three or more months.

Keratosis.—Keratosis and pre-epitheliomatous growths seem to yield to the x-rays, Williams's experience in these cases having been quite satisfactory.

Leprosy.—Sequeira produced marked improvement in cases of nodulated leprosy, but neither Scholtz nor de la Camp obtained any marked result.

Lichen Ruber Planus.—Scholtz observed from the use of the x-ray in this disease, retrogression of the papules, scaling and pigmentation.

Lupus Erythematosus.—Cures have been reported after five and more exposures of from ten to thirty minutes each, given about twice a week. The tube may be at a distance of 10 centimeters (4 inches).

Lupus Vulgaris.—The length and frequency of sittings must depend upon—(1) The resistance and (2) the distance of the tube, (3) the patient's susceptibility, and (4) the part treated. The tube may be placed at a distance of from 10 to 15 centimeters (4 to 6 inches). In the beginning the sittings should not be given oftener than twice a week, and as a rule should not exceed ten minutes. They should be suspended at the slightest indication of irritation. The treatment should be begun early and be carried out for a long time and vigorously. Recoveries are not so frequent as in some other skin diseases, and are less readily induced when operative measures have been employed previously. Many cases of recovery or marked benefit have been reported, however, after from 12 to 68 and even 151 sittings.

Mycosis Fungoides.—Improvement has been reported. In two cases the tumors as well as the premycosic patches disappeared. New foci, however, appeared in other parts of the body.

Nævus Flammeus or Vasculosus.—Nevus is in most cases cured or greatly improved.

Pemphigus Foliaceus.—Temporary improvement has been observed.

Prurigo.—Definite or lasting results have not been obtained.

Psoriasis.—With the tube at a distance of 20 centimeters (8 inches), exposures of three to five and ten minutes' duration should be given daily or, more safely, every second day. Improvement may begin

within three days; and healing in the area treated may follow six to ten exposures. The entire front or back of the trunk, when covered by the disease, may be exposed at one time by placing a powerful tube at a distance of from 40 to 50 centimeters (16 to 20 inches). All cases of psoriasis are relieved by roentgenism, some—particularly the acute cases—more promptly than others. The results obtained are more satisfactory than those from any other remedy.

Sarcoma.—See under *New Growths*.

Sycosis Vulgaris.—The distance of the tube is 15 centimeters (6 inches) at first, reduced gradually to 5 centimeters. The duration of the sittings at first is five minutes, increased to fifteen minutes. After from seven to eleven sittings the hair is loosened and falls out; in the course of the next ten to twelve days all indications of disease disappear.

Syphilis.—The cutaneous lesions of lues are apparently not affected by the x-rays.

Tinea Sycosis.—Good results have been reported. In one case a radical cure was obtained after a single course of 21 sittings, the exposures lasting from five to fifteen minutes each and the tube distance being from 5 to 15 centimeters.

Trichorrhexis Nodosa.—Freund obtained improvement in one obstinate case. The apparatus comprised a 25-centimeter coil, worked from a supply-current of 6 to 8 ampères and 110 volts; hard tubes were used; the sittings occupied seven to ten minutes each, and the tube distance was 10 centimeters.

Diseases of the Sensory Nerves

Neuralgia.—Stembo succeeded in relieving 21 out of 28 cases of neuralgia, giving from 3 to 10 sittings. In obstinate cases of trigeminal neuralgia at least temporary relief has followed daily exposures of half an hour. Caution must be exercised in these prolonged sittings.

Pain.—The analgesic effects of the x-rays have been demonstrated repeatedly and have been made use of for the relief of the pain associated with various affections.

Pruritus Ani and Vulvæ.—Several clinicians have reported decided improvements in these affections.

Diseases of the Joints

Articular Rheumatism.—The joints should be covered with a woolen cloth and exposed for ten to twenty minutes to a tube at a distance of 50 to 60 centimeters (20 to 24 inches). Diminution of pain and swelling

has followed this treatment. Of 52 patients treated by Stenbeck, 40 per cent. were much improved, 40 per cent. felt subjectively better and 20 per cent. were apparently unaffected.

Diseases with Involvement of the Glands

Adenitis.—Williams has observed disappearance of glandular enlargements in some forms of adenitis, and especially in *tuberculous* cervical adenitis. As in this disease the patient does not usually suffer by delaying operative treatment, he believes that radiotherapy should always be tried, especially with girls, in cases in which an operation would leave an unsightly scar. In cases amenable to the treatment, some improvement should be expected within a month or six weeks. Not all cases can be benefited. The editor has even observed suppuration to be hastened in tuberculous cervical glands under x-ray treatment by an expert operator. Morton's fluorescing method is said to give good results in many cases.

Goiter.—Enough improvement has been reported in uncomplicated cases of enlarged thyroid gland to encourage a further trial of the x-ray in this disease.

Hodgkin's Disease.—Exposure for ten minutes three times a week, with the tube at a distance of 20 centimeters, over each of the affected glands causes rapid improvement at first. In some cases the improvement has continued up to a recent date of report, but in others it has not been lasting. In these cases Morton's fluorescing method may be tried (see pages 151 and 170), or eosin may be painted on the skin over the glands. Arsenic should be given internally.

Leukemia.—Several cases of splenomedullary leukemia have been treated, with varying success, some being reported as cures and one as a symptomatic recovery. Others have been failures. One patient died suddenly while apparently improving. In other cases the patients remained apparently well many months after treatment had been discontinued. The period of treatment has been from six to twelve months. Low vacuum tubes are used at a medium distance, with caution at first, the time and frequency of exposure being increased gradually. As a rule, the applications are given on alternate days, at first for five minutes, later for ten minutes or longer, according to the patient's susceptibility. In one case exposures were made at first twice weekly over the spleen, then daily over the spleen, the ends of the long bones and the sternum.

In two cases of the editor's, exhibited at clinical lectures but not yet reported, great improvement is manifest after three and six months' treatment, respectively. The patients are given fluorescin internally

according to W. J. Morton's method (20 drops of a solution of fluorescin in water 1:60, thrice daily, ninety minutes after meals) and exposed to the radiations from a low-vacuum tube, at a distance of 12 inches from the spleen, for ten minutes at a time, thrice weekly. In one case, red cells have increased from less than 3,000,000 to 5,000,000; leukocytes have decreased from 850,000 to 34,000; myelocytes have disappeared. The lower border of the spleen, which had extended below and to the right of the umbilicus, has receded to within two fingers' breadth of the costal margin. General nutrition is good and the man is able to work, reporting to the out-patient clinic of Jefferson Medical College Hospital for treatment. In the other case the diminution of the spleen, though great and continuing, is not yet so marked. Hemoglobin from 34 per cent. has risen to 85 per cent.; red cells have increased from 2,300,000 to 3,900,000; white cells have fallen from 325,000 to 12,200; and myelocytes have decreased from 20 per cent. (65,000) to 8 per cent. (976).

Diseases of the Eye

Blepharitis.—Freund, after repeatedly observing cures of a co-existing blepharitis in patients under x-ray treatment for other conditions, treated three uncomplicated cases. As a rule the diseased region reacted after 4 to 9 weak irradiations of the closed eye with the use of hard tubes, the skin becoming healthy. The eye-lashes did not fall. No after-treatment by drugs was necessary. The accompanying conjunctival catarrh improved rapidly after the cure of the blepharitis.

Conjunctivitis and Keratitis.—Williams believes it to be quite possible to expose the *conjunctiva* to the x-rays for therapeutic purposes. He also reports a case in which the *cornea* was so exposed, with beneficial result. He raised the upper lid of the eye by sticking to it one end of a strip of surgeon's plaster, the other end of which he fastened to the forehead. He then suspended in front of the eye a disk of glass about 4 centimeters in diameter, in the center of which there was a hole 3 or 4 millimeters in diameter, so that the opening came opposite the area he desired to expose to x-rays. The disk was held by a thread which passed through its opening and was fastened to the surgeon's plaster on the forehead. The diaphragm used in the tube holder had an opening of about 1½ centimeters in diameter. This opening was brought opposite the aperture in the disk and only three centimeters away from it. The exposures were made once a week for three months and then twice a week for two months, lasting usually about ten minutes. At the end of this period there was a marked improvement in the scar and vision.

Tuberculosis

Glands.—See under **adenitis,** page 169.

Joints.—Marked improvement and apparent cure have been reported. In one case the exposures were given for two hours two or three times a week. In another the joint was treated ten minutes every day for two and a half months.

Larynx.—Laryngeal tuberculosis has been treated with varying success, many of the results being very disappointing.

Lungs.—Improvement has been reported in some cases of chronic pulmonary tuberculosis. Morton has seen benefit from his fluorescing method. The evidence is not yet sufficient to warrant a definite opinion, but it is probable that roentgenism may prove to have a place among useful secondary measures of physiologic therapy in tuberculosis of the lungs.

Peritoneum.—Daily exposures of thirty minutes' duration should be given with the tube at a distance of from 13 to 20 centimeters (8 to 5 inches). Favorable results have been reported in cases of chronic tuberculous peritonitis; in one case, after fifty exposures, the ascitic fluid had been absorbed, the hard tuberous masses which had been felt in the abdomen had disappeared and the general well-being of the patient had improved.

Sinuses.—Discharging tuberculous sinuses have been improved and in some cases recovery has been observed.

Wounds.—There has been reported a case of tuberculosis in a wound caused by a burn, in which recovery was established after three weeks' treatment.

New Growths

It is impossible at the present time to make a definite statement as to the therapeutic value of x-rays in the various forms of new growths. Different forms of neoplasm respond differently to irradiation. The action of the rays is to destroy the morbid cells, thus permitting healing to take place by normal reparative processes. Superficial growths are readily influenced by an exposure not otherwise detrimental and most of the small external cancers can therefore be treated by this method. Extensive or deep-seated growths must still be submitted to the knife. Roentgenism may then be used in the attempt to prevent recurrence. In recurrence, especially when extensive, or in cases that are already beyond surgical relief when they come under observation, life may be prolonged and suffering lessened by the intelligent use of x-rays.

Carcinoma.—*Small external growths* are first treated with the tube at a distance of 20 centimeters, shortened to 15 centimeters (6 inches) should there be no reaction after a few exposures. The duration is from five to ten minutes at first and should be shortened if too much reaction be excited. The exposures should be given not oftener than three times a week.

A glass speculum, painted on the inside with white lead, may be used in treating new growths in the *mouth and other cavities*. A sheet of pure tin with an aperture for the speculum to pass through acts as a further protection.

A growth on the wall of the *auditory canal* was treated by Williams through a speculum of which one lip was made of aluminum and the other of silver, the former permitting the rays to pass through, the silver protecting the healthy part of the canal.

When the growth is on the *eyelid*, the silver wire speculum used by ophthalmologists may be modified by soldering a piece of metal across that portion of it which goes under the lid. This, inserted under the part of the lid occupied by the new growth, will protect the eyeball from the rays.

Cancer of the breast is the usual form of the larger external growths. No matter how small the growth when discovered, and *a fortiori* when the primary growth is large, a thorough surgical operation should first be done. X-rays may be applied (through the bandage if necessary) while the wound is healing. Roentgenism should always be used as a post-operative treatment. It should be resorted to early in cases of recurrence after operation, the question of another operation, should the recurrent growth obtain some size, being determined for each case. In treating this condition it may be necessary to make the exposures as long as the skin will bear, even sometimes exciting a slight dermatitis. Inasmuch as the x-rays soften the mass and cause it to be slowly absorbed, caution must be observed lest symptoms of toxemia arise in cases in which the products of the tissue changes thus set up cannot find a ready outlet to the surface. In such cases drainage may be obtained by producing a small spot of ulceration with the x-rays, or by incising with a knife. Cases in which there is a large open ulcerating surface permit the greatest length of exposure. This energetic treatment softens the induration and causes profuse discharge, improvement taking place quite rapidly after the mass has thus been disposed of. Patients are quite likely to mistake this therapeutic ulceration and softening for an ill result and, in consequence, to cease treatment prematurely, complaining that they have been injured.

Not only should the diseased breast be exposed, but also the axillary glands, the whole shoulder and neck and the other breast.

After cessation of treatment patients should report for examination monthly for some time.

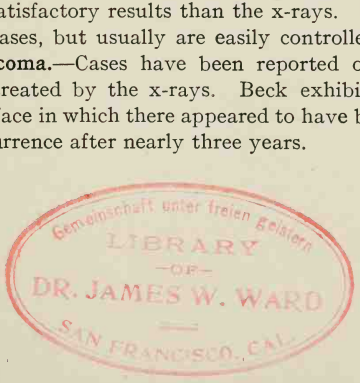
In inoperable cases, or when operation is refused, x-ray treatment may ameliorate suffering, prolong life and occasionally even check the spread of the growth.

Internal Cancer.—During this stage of development of the use of x-rays in internal cancer it is impossible to make any definite statement. In some cases the treatment affords relief after operation and good results of greater or less degree have been reported by competent observers in some cases in which operation was not practicable. Sometimes, especially in cancer of the uterus, it would seem as if actual healing was brought about. As yet, however, there has not been sufficient time to demonstrate the permanence of results, nor is the number of cases carefully reported sufficient to warrant positive conclusions.

As surgery is almost entirely hopeless in many cases of internal carcinoma, for example in growths of the cardiac portion of the stomach, attempts to develop radiotherapy in these affections are not only justifiable but necessary.

Rodent Ulcer.—The experiences of different observers in the treatment of rodent ulcer vary somewhat. The moist ulcerating forms heal more readily than do the dry, hard, indolent forms with hard, raised, worm-like edges. The latter often are a source of great trouble, a small remaining corner sometimes being left that is very difficult to heal. Infiltration of the cartilage, especially of the nose, and involvement of the bone and the pericranium are unfavorable conditions. In causing the hard edge of the growth to disappear the actual cautery may give more satisfactory results than the x-rays. Slight recurrences appear in some cases, but usually are easily controlled.

Sarcoma.—Cases have been reported of improvement in sarcoma when treated by the x-rays. Beck exhibited a case of osteosarcoma of the face in which there appeared to have been complete recovery, with no recurrence after nearly three years.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COUNTERIRRITATION—EXTERNAL APPLICATIONS—BLOODLETTING

BY

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COUNTERIRRITATION: *Mode of Action; Vascular Derivation; Reflex Nervous Influence; Friction; Liniments; Mustard Plaster and Poultice; Turpentine Stupe; Iodin Blisters; Setons; Fixation Abscess; Dry Cupping.* EXTERNAL APPLICATION OF HEAT AND COLD.—*Application of Heat: Hot Foot-bath; Hot-water Bag; Japanese Hand-stove. Moist Heat: Antiseptic Poultice; Uses of Moist Heat. Application of Cold: Cold Compress; Ice-bag; Leiter's Coils; Evaporating Lotions; Irrigation; Uses of Cold Applications. Soothing Applications and Lotions.* LOCAL BLEEDING: *Wet-cups; Leeches.* VENESECTION: *General Indications; Technic.*

COUNTERIRRITATION

Mode of Action.—Although counterirritation in various forms has been used for generations, we know very little of the exact mechanism by which it accomplishes its object. While we know that the application of an irritant to the skin cannot extract any *materies morbi* from the underlying tissues, we do not as yet fully understand what takes place in the deeper parts when either irritating or soothing applications are made to the surface. Unfortunately the question lends itself but poorly to experimental solution, as the manipulations in themselves affect both the superficial and the deep tissues, thus obscuring the interpretation of results obtained experimentally. Empirically it has been found that in some way the application of soothing or irritating substances to the surface undoubtedly relieves discomfort and apparently hastens the return to the normal condition in parts situated even very far below the surface. (See Volume IX, p. 19.) The effects produced on the deeper parts are due either to changes brought about in the circulation directly through the contiguity of tissues or in some other way, or to a reflex nervous in-

fluence either upon the tissues themselves (trophic) or upon the blood-vessels of the tissues, the skin surface and deeper parts (vasomotor). It is conceivable that disease of structures fairly near the surface, such as the muscular masses and certain portions of the skeleton,—mastoid process and tibial crest,—might possibly be influenced directly by applications made to the overlying skin. It is, on the other hand, inconceivable that any application which we could make to the surface of the chest or abdomen could act, because of its proximity, upon the tissues and organs lying within the abdominal or thoracic cavity

Vascular Derivation.—Counterirritation might act by diverting to a superficial area of the skin a portion of the blood of an organ in the interior; it could do so, however, only when the blood supply of the superficial and of the deeper parts is derived from the same source, or when there is a direct vascular communication between the skin and the deeper organ. We know that the parietal layers of the pleura, of the pericardium and of the peritoneum receive blood from the arteries coursing through the walls of the cavities which they line, while the organs contained within the cavities lined with these membranes receive their blood supply more or less directly from the aorta. Rénaut has apparently proved a direct vascular connection between the kidneys and the skin overlying them; yet the main blood supply of the kidney must be derived from the renal artery, which leaves the aorta at a point near, but entirely distinct from, the point of origin of the blood-vessels that supply the skin of the loin. Therefore, even though it might be true that change in the vascular condition of the skin overlying the kidney would somewhat increase the activity of this vascular connection between the organ and the overlying skin, it cannot be conceived that the volume of blood passing through these connecting vessels could have any appreciable effect upon an organ which obtains its main supply from so large an artery as the renal. Moreover, such connection between the superficial circulation in the skin and that of deeper organs has never, so far as I can find, been demonstrated except by this work of Rénaut. The subject of **correlated vascular areas,** that is, the relations between the blood-vessels of deeply seated organs and overlying or adjacent cutaneous vessels, and of **cutaneous reflex areas,** the association through nerve-trunks and centers of the internal viscera with certain cutaneous areas, is treated in another volume of this series (Volume IX, p. 253 *et seq.*). The accompanying illustrations (Figs. 18, 19, 20, and 21) should be studied in this connection, and compared with Figs. 22 and 23 and the table on page 169, showing the relation between cutaneous, central and visceral nerve supply.

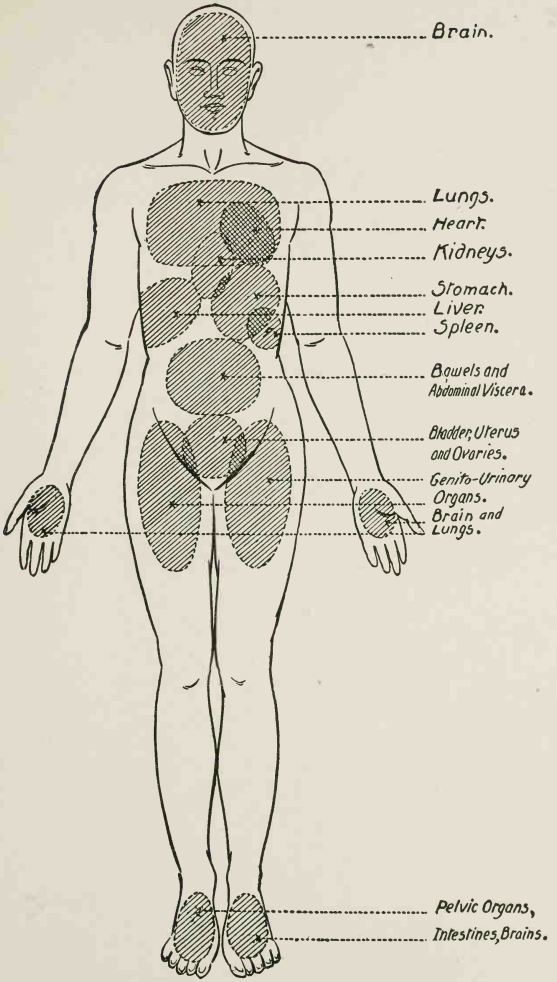

FIG. 18.—ANTERIOR CUTANEOUS AREAS REFLEXLY ASSOCIATED WITH INTERNAL PARTS.

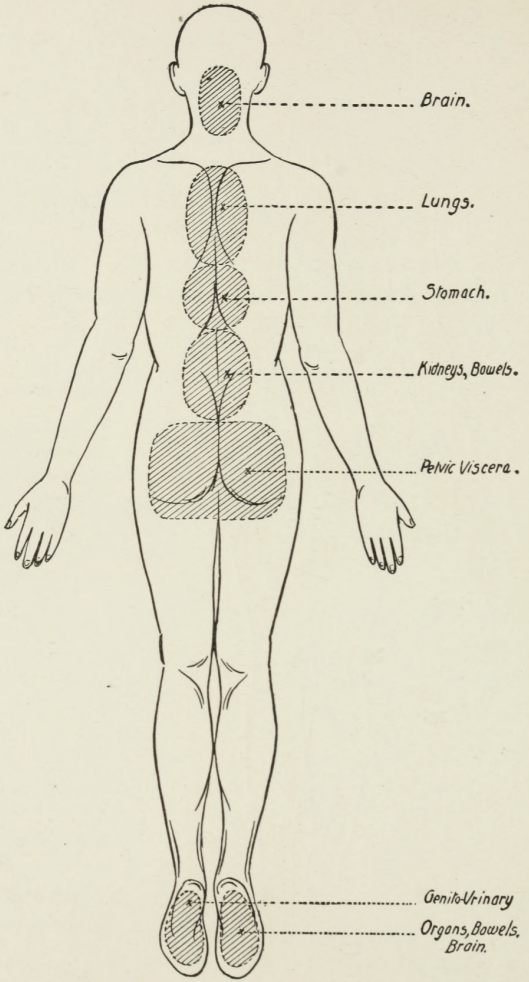

FIG. 19.—POSTERIOR CUTANEOUS AREAS REFLEXLY ASSOCIATED WITH INTERNAL PARTS.

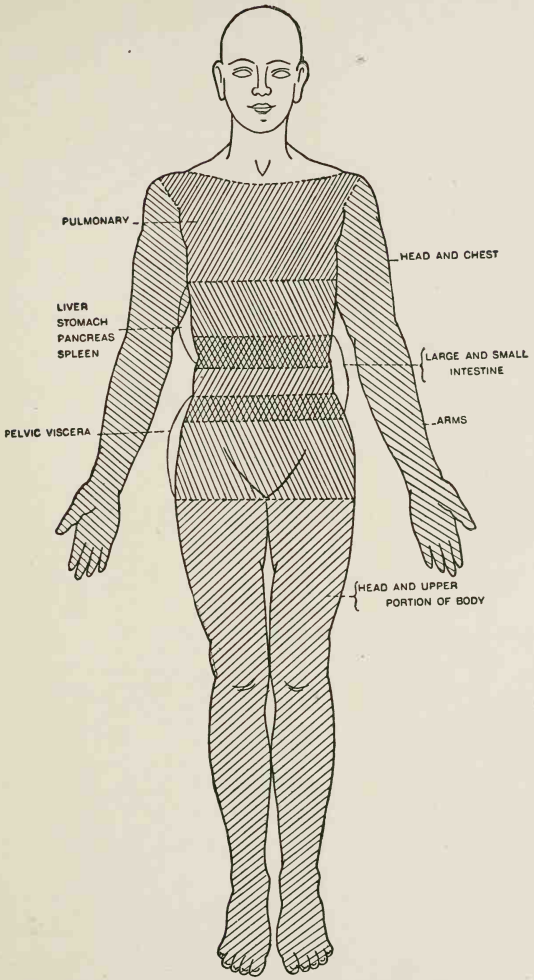

FIG. 20.—CUTANEOUS VASCULAR AREAS COLLATERALLY RELATED WITH THE VESSELS OF THE VISCERA (FRONT VIEW).

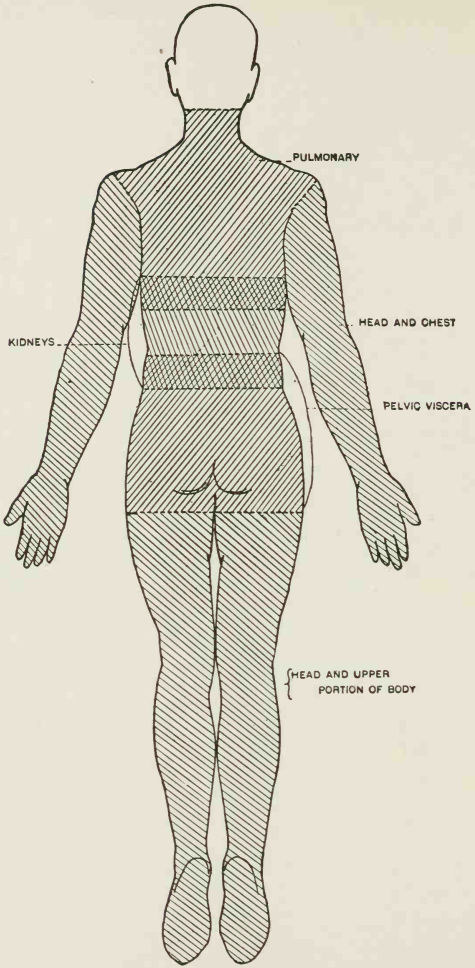

FIG. 21.—CUTANEOUS VASCULAR AREAS COLLATERALLY RELATED WITH THE VESSELS OF THE VISCERA (BACK VIEW).

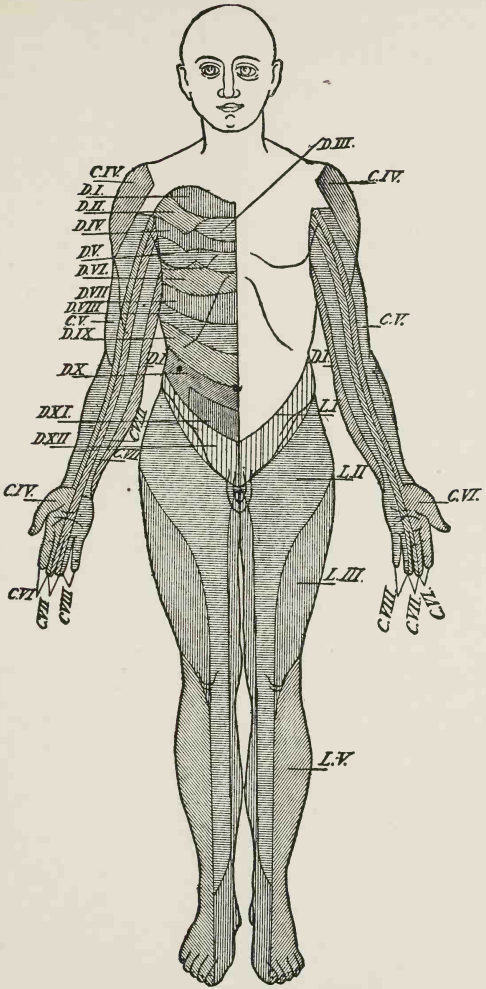

FIG. 22.—DIAGRAM OF SKIN AREAS CORRESPONDING TO DIFFERENT SPINAL SEGMENTS. ROMAN NUMERALS REFER TO NERVES.—(*From Tyson, after Starr. Trunk Areas from Head.*)

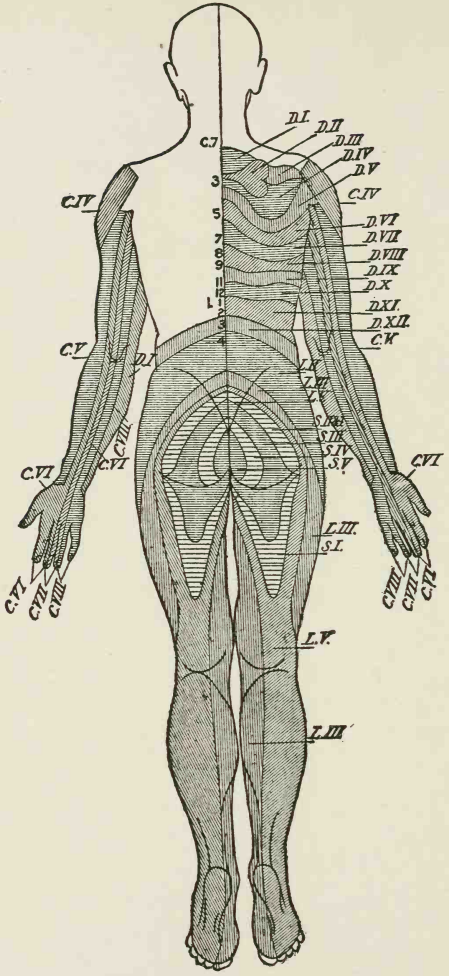

FIG. 23.—DIAGRAM OF SKIN AREAS CORRESPONDING TO DIFFERENT SPINAL SEGMENTS. ARABIC NUMERALS REFER TO VERTEBRÆ, ROMAN TO NERVES.—(*From Tyson, after Starr. Trunk Areas from Head.*)

In many instances the application of a counterirritant to an area of the skin, supplied by an arterial trunk totally different from that supplying a deeper-seated organ, certainly seems to produce marked

TABLE GIVING THE VISCERA THAT ARE RELATED TO THE VARIOUS SKIN AREAS SHOWN IN FIGURES 22 AND 23.

	Heart.	Lung.	Stomach.	Intestine.	Rectum.	Liver and Gall-bladder.	Kidney and Ureter.	Bladder (Mucous Membrane and Neck).	Bladder (Overdistention and Ineffectual Contractions).	Prostate.	Epididymis.	Testis.	Ovary.	Appendages.	Uterus (in Contraction).	Uterus (Lower Segment and Os Internum).
D1	×	×														
D2	×	×														
D3	×	×														
D4		×														
D5		×														
D6			×			×?										
D7			×			×										
D8			×			×										
D9			×	×		×										
D10				×		×	×			×		×	×		×	
D11				×			×		×	×	×			×	×	
D12				×			×		×	×?	×			×	×	
L1							×		×		×			×	×	
L5										×						
S1								×?		×						×?
S2					×			×		×						×
S3					×			×		×						×
S4					×			×								×

relief from symptoms due to congestion of the organ. In this case the ability to influence the quantity of blood going to the organ would presumably be in proportion to the length and complexity of the vascular connections between the point of irritation and the viscus. For example, it is theoretically inexplicable that the dilatation of the superficial blood-vessels at the nape of the neck should have much influence on the volume of blood going to parts supplied by the internal carotid artery, yet clinical experience seems to show conclusively that a decided influence may be exerted by means of such an application.

Reflex Nervous Influence.—If counterirritation does not produce its effect directly through the contiguity of tissue or by depriving a deep-seated organ of a certain proportion of its blood supply, an explanation of the results of counterirritation must be sought in the only other connecting link between the two parts, namely, the **nerve paths.** The reflex arc through which an effect upon the deeper blood-vessels may be produced by applications to the skin must consist of an afferent spinal nerve, a hypothetic vasomotor center in the spinal cord and an efferent impulse to the deeper blood-vessels, transmitted by branches of the sympathetic nerve emanating from the cord at about the same level. That such a reflex vasomotor arc exists is well recognized; and while the precise effect of applications to the skin upon the vessels of the underlying organs cannot be stated in definite terms and is not capable of ocular proof, the clinical results of such applications are almost equivalent to ocular demonstration. The best illustration of the modification produced in the deeper circulation by changes in the condition of the blood-vessels of the skin is seen in cases of inflammation of the extremities, in which the application of heat or cold to the surface is capable of giving immediate relief from pain due to inflammation of the deeper portions. In periosteitis or osteitis of the phalanges the relief from tension is so marked that the patient will almost instinctively apply moist heat externally. Of course, in this situation it may be that the tension is relieved partly because the portion of the blood ordinarily destined for the deeper parts is diverted into the superficial vessels; but a more rational explanation is found in the assumption of some reflex vasomotor effect upon the deeper vessels. It is possible that the external application of heat hastens the flow of lymph in the part, and that the increased activity of the lymphatic circulation may, at least in part, account for the relief of tension. The explanation is, however, difficult to prove or disprove. (See Volume IX, p. 246.)

Whether the change produced by the superficial application of counterirritants is due to changes in the vascular supply of the skin and

a consequent influence upon the circulation in the deeper parts, or whether it is due to a subsequent reflex vasomotor action upon the vessels is not certainly known and does not appear to be susceptible of definite proof. By clinical experience it is found that the application of irritants to the surface of the skin is followed in some cases by a favorable effect upon the pathologic process going on below.

Friction.—The simplest form of counterirritation is friction. It is possible that some of the good results following its use are due to the massage to which the parts are incidentally subjected; that this is not entirely true, however, is shown by the fact that the effect of friction may be enhanced by the use of some stimulating or irritating substance. For instance, in the condition ordinarily known as **lumbago,** if some mildly irritating application, such as chloroform liniment, turpentine and sweet oil, or any of the liniments that are in such common use, be employed, a sense of warmth in the skin is experienced and the discomfort in the deeper tissues is coincidentally relieved. In cases in which friction with an irritating agent gives relief the same end can be attained by applying the irritant without friction. Of the latter, the ordinary **mustard plaster,** the **mustard poultice** and the **turpentine stupe** are the means in most common use. For the mustard poultice one part of mustard is usually mixed with two to five parts of some diluent, such as flour or flaxseed, according to the patient's age and tenderness of skin, and the mixture further mitigated with glycerin and white-of-egg when the application is to be prolonged. The element of friction obviously does not enter into the action of these applications, and we must consider that their good effect is due, in part at least, to the dilatation of the cutaneous blood-vessels which they effect. In less acute conditions, and especially when partial or complete organization of the inflammatory material has taken place, the application of **tincture of iodin** as a pigment has been used for so many years that its position as a therapeutic agent is unassailable, even though we do not precisely understand its mode of action. The iodin compounds have been for years looked upon as sorbifacients; and although many deny them any action of this kind, save in syphilitic inflammation, the mass of clinical evidence to the contrary is too overwhelming to be ignored. Whether the iodin acts simply by producing a continuous hyperemia of the skin, or whether the favorable results are due to its effect upon the terminal nerve filaments, or whether the drug is absorbed and possesses the power to diminish exudation, cannot be asserted positively.

Blisters.—The question whether blisters are beneficial or harmful has for years occupied the attention of therapeutists. While undoubtedly

the employment of blisters has been much overdone in the past, there is such a mass of clinical evidence bearing upon their value that they must be considered as having a rightful place in our pharmacopeia. The **dangers** of blisters are threefold: In the first place, the action of cantharides—which is the only blistering material that at the present time deserves consideration—may be too vigorous, and instead of having simply counterirritation, we may actually have destruction of the vitality of the skin. This is sometimes seen in the case of very young children and in those who are much debilitated. Fortunately, however, blisters are seldom necessary in these cases. The **age-limit** at which blisters become available with safety cannot be stated definitely; yet it seems to me that the rule to avoid their application in those under seven or eight years of age is one that should be observed. A second danger from the use of blisters—and one to which much attention has been given—is the irritating effect of cantharides upon the kidneys. While in some of the elaborate discussions at meetings of societies in various parts of the world a few cases of **renal irritation** following promptly upon the application of a blister have been reported, these results are so rare that the use of blisters need not be viewed with apprehension in those whose kidneys are healthy. It may be objected that in many cases it is impossible to tell from examination of the urine whether the kidneys are normal or not; but by a careful consideration of the daily quantity of urine and of its specific gravity, and the presence or absence of elevation of arterial pressure, a just estimate of the condition of the kidneys can usually be made. The third objection is one to which little weight need be attached, providing proper care is taken before and after the application of the blister. It has been asserted that the seat of vesication is a point where **infection** can readily occur. By care in cleansing the skin before the blister is applied and by the proper treatment of the blister after it has developed infection can practically always be prevented. At the present time the prolongation of the irritation produced by a blister, as by the use of irritating ointments of various kinds, is entirely abandoned; although it is not many years since some of the irritating ointments contained in the pharmacopeia were used for the same purposes as were the now abandoned setons. The large blisters that were formerly much in vogue are being almost entirely superseded by blisters of smaller size, applied at short intervals; and instead of the blisters being kept from healing, they are now made to heal as rapidly as possible. It will usually be found that a blister **one inch square,** repeated as often as may be necessary, will answer the purpose better, will heal more rapidly, will be less

apt to be followed by irritation of the kidneys and will less frequently become infected, than those of larger size.

Uses.—At the present time the chief use of blisters is in certain forms of **chronic arthritic troubles.** Massage and hydrotherapy are, however, now being used to a greater extent and with more advantage in cases of this kind. In various **inflammations of serous membranes** that cannot be relieved completely by operative measures blisters are still used at times. A typical example of such an indication for the use of blisters is found in **obstinate and prolonged pleural effusion.** A more rational mode of treatment is the frequent use of the aspirating needle. In **pericarditis with effusion** blisters are still considered by some the best method of limiting the inflammation. The most vigorous advocate of this method of treatment is Caton, who advises the employment of repeated small blisters over the upper portion of the chest on both sides to prevent inflammation of the heart in all cases of **rheumatism.** The results reported by him are certainly very favorable; yet it is a question whether they were not due more to his care in keeping his patients absolutely at rest for a long time after the subsidence of all acute symptoms. The former practice of applying large blisters to the head—even converting the whole scalp into one huge blister—has now been practically abandoned save by a few. The discomfort accompanying such extensive vesication, the large quantity of cantharides that may be absorbed from so large a surface, which is also difficult to keep aseptic, are strong arguments against the practice, in spite of the fact that marvelous cures of **meningitis** were at one time attributed to the production of such extensive areas of counterirritation. In one other condition blisters find a place; although here, as in other cases, it is difficult to weigh their value exactly. In certain **long-standing cases of indigestion,** without evident organic disease of the stomach, a small blister applied to the epigastrium is frequently followed by relief. It has been said that this relief is due to suggestion; yet it cannot be denied that, through the sensory spinal nerves and the sympathetic nerves going to the stomach and their connections within the spinal canal, the stimulation of the skin may have some effect upon the wall of the stomach. It is a clinical fact that after the application of the blister to the epigastrium or over the middle thoracic vertebra there is oftentimes seen a decided improvement in obstinate cases of gastric indigestion not due to organic lesion or perversion of secretion within the stomach. [Mild, superficial linear cauterization with a Paquelin point sometimes answers better.]

Blisters are also used in the treatment of **iritis.** A row of small

"flying blisters," about half an inch square, applied at intervals of twenty-four hours to the temple corresponding to the affected eye, greatly assists in reducing the inflammation and lessening the pain.

[In the treatment of **pulmonary tuberculosis** blistering has a useful place. Small blisters applied over and around areas of softening at intervals of three or four days, one being allowed to heal before the next is applied, and a quadrant of the chest gradually covered in this way in the course of several weeks, tend to relieve cough and pain and seem also to aid in promoting healing. Sometimes it is well not to open the blister, but to protect it and allow the serum to be reabsorbed. Over cavities, also, they may be used similarly. In the treatment of **unresolved pneumonia,** croupous or catarrhal, 'flying blisters'—that is to say, a succession of small blisters, permitted to produce but mild vesication and gradually applied over a half or the whole of the anterior or posterior aspect of the chest, or over and around the area or areas of persistent consolidation—have not only tradition, but well-attested recent experience, to commend them.]

Mode of Application.—The best method of applying a blister is as follows: The skin is carefully cleansed with soap and water and then with alcohol or some other antiseptic, and, in some cases, moistened with vinegar, after which the blistering plaster is applied and allowed to remain in position for from **four to eight hours.** To remove the plaster, the edges are carefully separated from the skin on all sides; by gentle elevation of opposite sides of the blister, without lateral traction, it can usually be removed without breaking any of the vesicles. Ordinarily, when the plaster is removed, the epiderm is not uniformly raised by exudated serum, but there are seen larger or smaller bullæ separated by areas of very hyperemic skin. The application of a moist aseptic dressing over the blister will soon cause the exudation of serum to such an extent as completely to fill the raised epidermis. Three courses are then open to us: first, to allow the blister to dry; second, to puncture the skin, let out the serum, allow the epidermis to fall back into place, and then protect the surface with a layer of aseptic absorbent cotton or gauze, sometimes with the addition of a bland, aseptic unguent; or, third, to apply to the denuded surface an irritating ointment. The second of these methods would seem to have all the advantages with none of the disadvantages of the other two, while after such a treatment of a blister there is no pain and the rapid healing allows of a repetition within a few days.

Setons.—The use of setons has been practically abandoned, partly, no doubt, because of the fact that we now realize that any suppurating

infected wound is a source of imminent danger. With our present knowledge it seems remarkable that there are so few instances recorded in which grave septic results followed their application. There are one or two points that theoretically would strengthen the idea that setons might be of value. One of these is the fact, frequently observed, that in certain individuals with high arterial tension and other clinical manifestations, which, grouped together, characterize the so-called plethoric type, any long-standing discharge seems to a certain extent to act as a safety-valve, the cessation of which is sometimes followed by increasing discomfort, if not by actual damage. The other point somewhat in favor of the use of setons, or rather explaining the good effects at one time attributed to them, is the comparatively recent discovery of the apparent value of aseptic abscess formation by the injection of oil of turpentine into the thigh in cases of pneumonia ("fixation abscess"). The advisability of this procedure has, however, not as yet been definitely granted, and the employment of such a measure smacks rather of the old-time reasoning which is now known to be fallacious, than of modern or rational and less vigorous therapeusis.

[Very recently, however, Brocq has reported two cases from his practice in which excellent results appeared to have followed the use of the issue. One patient, seventy-two years old, had suffered from gout and arteriosclerosis for twenty years and there were signs of beginning mental degeneracy. He developed bronchitis, became somnolent and apathetic, and his general condition caused serious anxiety. At this time he burnt himself accidentally, and the wound continued to suppurate notwithstanding the careful dressings used; but the general condition of the patient improved and his intelligence recovered its lucidity. He wished to have the wound closed, and this was done; but in a few days the general condition began to get worse, and after consultation with the family physician it was decided to put a cautery or issue on the arm. This was followed by immediate improvement in the general condition. The other patient was an asthmatic whose condition had grown steadily worse for four years, and who had shown all the morbid signs of generalized arteriosclerosis with edema of the lower limbs, albuminuria, phlebitis, and emboli causing pulmonary infarct several times. He had had an attack of apoplexy, with loss of consciousness, aphasia and right hemiplegia, and at a subsequent time exhibited symptoms of intestinal obstruction. The treatment consisted in a well-nigh complete milk regimen, some castor oil every morning, from 25 to 50 centigrams of quinin hydrochlorate, dry cupping and the use of the actual cautery, and sometimes wet cups. During an

attack of epilepsy a nurse gave him an injection of ether which produced an eschar 4 to 5 centimeters long and 3 centimeters wide. Suppuration set in after ten days and the patient began to improve. After three months the cavity beginning to heal and the patient's condition having become worse, an issue was made on the left arm. Whenever this issue does not suppurate well, the patient's health declines. Cases of this nature cannot, however, be of frequent occurrence.]

Fixation Abscess.—The fixation abscess, so called by Fochier, who employed it first in the treatment of puerperal fever,—"the type of pyogenic diseases,"—has been exploited as a therapeutic device chiefly by French clinicians, but in recent years has also attracted some attention in this country. The difficulty of judging the value of a comparatively untried therapeutic method is in this instance enhanced by the circumstance that it is a heroic one, limited in its applicability, and recommended even by its supporters only in grave cases of infectious diseases with a tendency to the formation of pus. The best results are said to have been obtained in puerperal fever, probably because the subjects are in the vigorous period of life and the disease runs a rapid course, so that grave symptoms call for the most radical measures before there has been time for a general lowering of the resistance. "It is a most useful method in certain desperate cases of **pneumonia, bronchopneumonia** and **puerperal fever,** and has been employed with some success in various other infectious diseases and in some cases of poisoning. It is, however, to be regarded as an exceptional procedure, because it is in many cases very difficult of application" (Charles).*

Many theories have been advanced to explain how the fixation abscess influences the course of the disease. Of these, the simplest and most plausible appears to be that which has given the method its name: the microörganisms in the blood migrate toward the artificial lesion, as we know they migrate toward natural lesions or damaged organs, and become encysted or 'fixed' in the abscess. That such migration toward the fixation abscess actually takes place has been proved for the pneumococcus and the streptococcus in pneumonia and puerperal infection respectively (Cole), as well as for the typhoid bacillus (Duvergey). Very soon, however, the pus becomes sterile,—hence the term 'aseptic abscess' sometimes employed,—partly on account of the antiseptic power of the turpentine which is employed to produce the abscess, and partly owing to general factors—phagocytosis, the action of bacterial toxins—which become operative in the case of all abscesses after a certain time.

* "Les abscès de fixation dans les maladies infectieuses et les intoxications," Paris, 1903.

It may be that in these latter factors the therapeutic explanation is to be sought; when modern researches on the chemical factors in immunity have progressed far enough, they may possibly shed light on the subject.

Technic.—After much experimentation with a variety of substances, both chemical and bacterial, **spirit of turpentine** is now generally regarded as the most suitable agent for the production of a fixation abscess. One or at most two injections of **one cubic centimeter** (fifteen minims) each are given hypodermatically, and, if no reaction takes place, must be repeated after from twelve to forty-eight hours. The most convenient site is the outside of the thigh, but any part well supplied with subcutaneous cellular tissue may be selected. Fochier advises that the injection be made near the site of the lesion. In ordinary cases diffuse painful swelling and redness of the part soon develop; after two or three days the swelling becomes more localized, and soon the pus begins to collect. This is the time for opening the abscess, which should not be allowed to go on to spontaneous rupture. In cases of diminished tissue-resistance the reaction is often delayed, and the abscess, when it appears, is a 'cold abscess,' with little pain and inflammation; in such cases incision should be delayed until another abscess has been started, especially if there is little sign of general improvement. Total absence of reaction is a grave prognostic sign and portends a rapidly fatal termination (Fochier). After incision the wound heals kindly in the space of about a week; neither irrigation nor drainage is, as a rule, required. The usual aseptic precautions must, of course, be observed both in the production and in the subsequent care of the abscess.

The conditions in which the use of the fixation abscess is said to be indicated have already been mentioned; but as the method becomes better known its range of usefulness may be considerably enlarged. It **should not be employed** in cases of chronic cardiac and renal disease with a marked tendency to edema, nor in the very old; while in the presence of symptoms of acute renal disease caution in its use is very necessary.

Dry Cupping.—The application of dry cups is of such long standing that there seems to be some empiric justification for its employment. While we now know that the use of such remedies cannot have any curative influence upon infectious processes in internal organs, the dry cup does undoubtedly deserve a permanent place in our armamentarium. The exact method of its action cannot be explained. The amount of blood actually drawn into the skin and subcutaneous tissues in the area covered by the cup would hardly seem sufficient of itself to produce a

very marked effect on the underlying organs. It is possible that through reflex nervous influence the application of the cup may have some effect upon the circulation of the organs in the interior of the body. Some support is given to this idea by the fact that the nerves of the skin overlying the viscera, and the sympathetic nerves which we believe to govern the blood supply of the latter, are derived from the same segment of the spinal cord.

Indications.—Whatever the explanation may be, it is a well-ascertained clinical fact that the application of dry cups to the surface has a marked effect upon the organs lying below. So frequently does it happen that the application of dry cups over the region of the kidneys in cases of partial **suppression of urine** is followed within a short time by free renal excretion, and that the application of dry cups over the base of the chest in the early stages of **pneumonia** and in congestion of the lungs from various causes relieves the pain and sense of oppression and enables the patient to take deeper and fuller breaths, that the result must be credited to the remedy. In certain **muscular troubles** the application of a few dry cups has a most happy and immediate effect. In **torticollis** and in **lumbago** relief may sometimes be seen to follow promptly on the application of a few dry cups over the painful muscles. It is possible that in these cases the dry cups do good not only by withdrawing blood from the underlying muscle, but also by mechanically stimulating the muscle-fibers, just as they would be affected by massage. Our knowledge of the actual pathologic conditions present in these 'muscular rheumatisms' is woefully lacking, considering the length of time they have been observed. It is probable that a large part of the discomfort and disability is due to congestion of the blood-vessels and serous exudation into the connective-tissue spaces in the muscle and around the nerve-endings. These conditions are best relieved by voluntary movements of the muscle, but such movements are so painful that it is with difficulty that the patient can execute them. Probably dry cupping acts, at least in part, as does massage, by mechanically emptying the muscular interspaces and the minute blood-vessels.

Of the two **forms of cups** in use,—those in which the vacuum is produced by mechanically withdrawing the air and those in which the air within the cup is rarefied by heat before application,—the latter are by far the more powerful, besides being more easily obtainable. When the pump of the mechanical cup acts perfectly, an equal extent of congested skin and subcutaneous tissue can be attained as with the old-fashioned cup. But the pump and the valves of the cups themselves are so easily thrown out of gear that the mechanical cup is by no means

satisfactory. The cups ordinarily sold in drug-stores, in which the vacuum is produced by the expansion of a rubber bulb, are almost useless, the rarefaction being too imperfect to cause much negative pressure. As good results can be obtained with an ordinary tumbler or wineglass as with the best cups made. It is important to see that the edge of the vessel used as a cup is perfectly smooth, in order, in the first place, that a good vacuum may be obtained, and, in the second place, that the patient's skin may not be lacerated by contact with the rough edge. The air may be heated by introducing a few drops of alcohol and placing within the cup a small strip of toilet-paper or other inflammable material that leaves a cool ash. The most convenient way is to pour into the tumbler about half a dram of alcohol, spraying it over the sides of the glass and throwing out the excess, and then wipe the edge of the tumbler dry, so that it may not get overheated. The alcohol is then ignited, and while it is still burning, the tumbler is quickly and firmly applied to the desired site. Almost at once the flame goes out, and, as the hot air contracts, the skin is drawn up rapidly and firmly into the tumbler. A successful cup should show a projection of a semicircular dome of purple skin with wide-opened sweat-ducts and areas of blood extravasation into the superficial layers of the skin. The cup should be allowed to remain for several minutes. It may then be quickly removed by inserting the thumb-nail beneath its edge to admit the air. If the cup is properly applied, the skin will be unbroken and no further treatment of the area will be necessary. After removal of the cup there should be left a large circular welt, giving a distinct sense of induration to the hand. The evidence may persist for days, and when the cup has been vigorously applied, the skin goes through changes precisely resembling those seen after any ecchymosis.

[**Digital Manipulation.**—Under the somewhat vague and misleading titles of 'manual therapy' and 'mechano-neural therapy' there has been brought forward lately a mode of treatment which is essentially a form of counterirritation—the irritant being applied in the form of manual, or rather digital, pressure. The latter is confined altogether to the muscular masses along the spine,—the erectores spinæ,—the theory on which the method is based being that, by altering the vascular conditions in the soft parts overlying the spinal column, an inverse change can be brought about in the vascularity of the spinal cord itself, whereby an influence is exerted on the internal viscera. Thus it is assumed that, when a section of the spinal cord is hyperemic, the soft parts overlying it are in a state of anemia; and, vice versâ, that anemia of the cord is accompanied by passive congestion and edema of the soft

parts. Again, the vascularity of the cord is assumed to bear certain relations to the vascularity of internal organs. When, for example, there is inflammation, and, therefore, active hyperemia of the lungs, the section of the cord which contains the controlling vasomotor mechanism for the lungs will, according to this theory, be in a state of hyperemia, because the active contraction of the pulmonary vessels demands the constant emission of impulses from the vasomotor centers in the cord. In conditions of passive congestion, on the other hand, when the muscular tone of the blood-vessels is relaxed, the vasomotor centers are said to send out fewer impulses and the blood supply to the cord is, therefore, diminished, in accordance with the physiologic law that increased function of a part demands an increased supply, and vice versâ. While this theory is ingenious and has some *a priori* arguments in its favor, it is not susceptible of actual proof and must remain at best a working hypothesis. However, its truth can to a certain extent be submitted to clinical test; for it obviously applies to diagnosis as well as to therapeusis. Whether, apart from its **suggestive** influence, the method will prove to be as useful as its supporters affirm, especially in the treatment of chronic visceral disease, must be left to the decision of time and practical experience. J. Madison Taylor has observed good results in conditions of **malnutrition** in children and in **vasomotor ataxia** and other functional nervous disturbances.

Granting the correctness of the underlying physiologic principles, it is obvious that the methods by which the desired effect is exerted on the spinal cord depend largely on convenience and on other purely external factors. Thus, in pneumonia, instead of applying cups to the chest, it is advised that they be applied to the lower cervical region; in dysmenorrhea the hot-water bag will actually in some cases give more relief when applied to the sacral region than when laid on the hypogastrium; habitual constipation from intestinal atony may be as successfully combated by manipulation of the back as by direct massage of the abdomen. The method recommended by manual therapeutists or mechanoneurotherapeutists is either constant or intermittent **pressure with the finger-tips** along the appropriate region of the back: constant pressure, when the object is to drive the blood out of the tissues, and intermittent pressure to induce hyperemia of the parts. The pressure is applied with the tips of four fingers, suitably curved and held in line. The degree of **force** to be used varies somewhat with the part of the column manipulated and the conditions present, but should never be great, as the object is solely to influence the vasomotor mechanism reflexly, not to act upon the muscles—or the bones—directly, as in the

case of massage. Similarly, the duration of the manipulations and their frequency must be determined for each individual case; it is important never to fatigue the patient. As a rule, a sitting of ten to fifteen minutes three times a week answers every purpose in chronic conditions, for which this method is chiefly recommended. Some of the 'cures' attributed to **'osteopathy'** are said to depend upon the application of this form of manipulation, the ostensible object of the treatment being to replace a supposedly displaced vertebra or rib.]

EXTERNAL APPLICATION OF HEAT AND COLD

The question whether to apply heat or cold cannot always be decided beforehand; every one has experienced the difficulty of determining in a given case whether a cold or a hot application will give more relief. Frequently it will be found that at one stage of the trouble the application of external heat is most agreeable and seems to do most good, while after a short time in the same case the application of cold is more beneficial. It is also difficult to explain this variability. Theoretically, it would seem that the two kinds of application ought to have precisely opposite effects as regards the deeper tissues. (See, however, Volume IX, p. 245.)

Application of Heat

The Hot Foot-bath.—Heat may be applied externally in a variety of ways. The simplest is, of course, immersion of the affected part in hot water. This, however, is but seldom practicable, except in the form of the old, well-known foot-bath, when it is desirable to influence not so much the part immersed as a congestive disturbance in some distant organ, such as the brain. The hot foot-bath probably acts in two ways: the most manifest effect is the dilatation of the vessels of the lower extremities, which, therefore, presumably contain more blood than ordinarily, thus diminishing the volume of blood in other parts of the body. A more general effect also appears to be produced by causing dilatation of all the arterioles in the body. The hot foot-bath probably acts well in both ways—for example, in **cerebral congestion** and in **epistaxis.** The favorable results of a hot foot-bath in both of these conditions, as well as in the early stages of a febrile reaction from any cause, are presumably, in part at least, due to the general vascular dilatation with consequent restoration of the equilibrium of the circulation throughout the body. [Another effect of the hot foot-bath when accompanied by a copious hot draught—*e. g.*, lemonade, tea or toddy—

and followed by a hot dry pack, is to provoke sweating—a useful means of "breaking up a cold," and especially applicable in the early stages of an acute coryza or of certain infections, as **influenza, rheumatism, measles, scarlatina,** or even **pneumonia,** not only for derivative, but also for eliminative purposes.]

Aside from its use in inflammatory conditions, external heat is frequently employed for the relief of **painful spasmodic affections.** While we do not at all understand in what way the result is accomplished, clinical experience extending over a long time shows that the external application of heat is of great advantage in certain spasmodic affections of the hollow viscera; as, for example, in **spasm of the intestine** and in **spasmodic contraction of the ureter and bile-ducts** in their efforts to rid themselves of calculi. External heat applied to the suprapubic region is also employed in cases of **urinary retention,** in which condition the application of cloths wrung out of hot water is frequently followed by evacuation of the bladder.

The Hot-water Bag.—The local application of external heat is most easily made by means of the hot-water bag, which is now made in a variety of shapes and sizes, suitable for application to the various parts of the body. Of course, the heat furnished by the hot-water bag can never exceed about 200° F. (93° C.). Another method is by the use of **Japanese hand-stoves,** in which the heat is generated by the slow combustion of a cartridge. An excellent contrivance for the dry heat is a bag filled with salt or builder's sand. Whether or not it is actually the case is difficult to prove scientifically, but the heat derived from the **hot salt bag** seems to have a greater degree of pungency than that obtained from any other source. For relieving the aching pains in the bones in the early stages of influenza the hot salt bag is a valuable palliative agent. **Leiter's coils** can also be used for the application of dry external heat, but they have the same disadvantage as hot-water bags, inasmuch as water cannot be heated above a certain temperature, with the additional factor that the water within the conducting tube is favorably placed for the rapid loss of heat.*

Moist heat can be applied locally in a variety of ways. The simplest method of application is the utilization of the body-temperature as a means of generating heat. Any medium, such as **cotton-wool** or **spongiopiline,** or even **patent lint,** placed in contact with the skin and covered with an impermeable material, such as **paraffin-paper, oiled silk,** or

* Other apparatus for the local application of dry heat, as electric and chemical thermophors, and notably the 'hot-air box' or 'baking apparatus,' are described in Volume IX, pp. 271–275.

rubber tissue, will soon abstract from the body a sufficient quantity of heat to have a marked local action upon the superficial vessels. The old-fashioned **poultice** has stood the test of experience too many years to be lightly discarded; it is probable, however, that there is no particular virtue in a poultice made from flaxseed beyond that to be obtained from the use of materials less untidy and better capable of being kept aseptic. [A well-made flaxseed poultice, prepared by thoroughly stirring together the meal and boiling water in successive small increments, spreading the mixture with a hot spoon on a layer of gauze (cheese-cloth) resting on a heated metal tray, and then covering with another layer of heated gauze, should retain its heat for three or four hours, should be light and should adapt itself well to the shape of the body. Outside of the poultice a layer of oiled silk or oiled paper should be placed. Poorly made poultices do more harm than good.] The so-called **antiseptic poultice,**—better called **heating compress,**—made by retaining the heat and moisture in a thick pad of gauze moistened with a weak solution of mercuric chlorid, seems to accomplish the same purposes as those for which the flaxseed poultice was used without any of the disadvantages of the latter. In addition to these advantages over the flaxseed poultice the heating compress is more easily prepared, more easily applied, and also possesses the virtue of lightness. For application to the chest in **acute bronchitis** or **catarrhal pneumonia,** for instance, two or three layers of patent lint, made in the form of a waistcoat and completely covered with oiled silk or rubber tissue, will answer the purpose fully as well as the old-fashioned cotton jacket, the weight of which interferes with the respiratory movements. In addition, the exposure necessitated by changing the compress is far less than when the old form of jacket made of linseed is employed.

Uses of Moist Heat.—The application of simple, moist external heat was much more in vogue in former times and is probably receiving less attention now than it deserves. While it is difficult to explain how surrounding the chest with a warm, moist dressing can bring about relief in deep-seated inflammation of the respiratory organs, such an effect is undoubtedly produced, as is evidenced not only by the increased comfort of the patient, but also by the lowering of the temperature and the slowing of the pulse and respiration after the jacket is applied. Considerable difference of opinion prevails in regard to the length of time that the poultice should be allowed to remain in contact with the chest. My own experience has been that whenever a jacket poultice is advisable in the treatment of deep-seated respiratory disease, its continuous application appears to do no harm and certainly to bring

about as good results as does its intermittent use. [The editor employs poultices during the day and a lamb's-wool jacket (carded wool) at night, to avoid waking the patient for change of dressing. With the lamb's-wool jacket a hot-water bag or other direct-heating application is often combined

While the advantage of moist heat in the form of an old-fashioned flaxseed poultice, or, better, the heating compress as just explained, or of dry heat in the form of a cotton or lamb's-wool jacket, has been too well proved by years of experience in **croupous pneumonia,** the same procedures are not to be advised in the **catarrhal pneumonia of children.** Here there are certain imperative indications to be met, which are not satisfied by the application of moist heat. The temperature is high and must be combated; the child is cyanotic and in constant danger of suffocation, hence remedies calculated to stimulate the respiratory center and deepen the respirations are called for. The cotton jacket or heating compress must, therefore, give way to the more stimulating and heat-abstracting **wet-pack,** either general or partial, or even to the **half-bath with affusions of cold water,** as set forth in the volume on Hydrotherapy. (See Volume IX, p. 139.)

Application of Cold

The application of external cold is constantly receiving more attention, partly, no doubt, because we realize that in most of the diseases accompanied by fever this phenomenon is due not to internal congestion or other action of cold, but to the presence within the body of toxins capable of causing fever. External cold can be applied locally in the form of **cold compresses** or the **ice-bag,** or by means of **Leiter's coils.** The chief disadvantage of compresses is the necessity of renewing them at short intervals, owing to the rapidity with which heat is absorbed. It is, therefore, necessary to have beside the patient's bed either a basin of iced water, or, preferably, a large cake of ice, one compress being kept on the ice while the other is applied to the part. Almost the only use of cold compresses at the present time is in certain inflammatory conditions of the eye.

External cold is also applied in various minor ailments, especially headache, by the employment of **evaporating lotions,** such as eau de cologne, alcohol, vinegar and water, or iced water.

Since the days of aseptic surgery **irrigation** by means of cold water is much less frequently employed than formerly; in fact, at the present time, it is seldom or never used.

The advantage of the **ice-bag** over the cold compresses is that it does

not have to be changed so frequently; it has, however, the disadvantage that even before the ice within it is thoroughly melted the temperature is decidedly raised. This disadvantage is not present when **Leiter's coils** are employed, owing to the fact that in the latter the constant flow of a fresh supply of cold water through the coil keeps the skin in the neighborhood at a uniform temperature.

One **drawback** to the use of external cold is the danger that in debilitated patients the constant application of cold may so impair the nutrition of the skin that its vitality may be lost, although in a previously healthy person suffering from an acute illness, excepting very old or very young individuals, cold applications can usually be kept up constantly.

Uses of Cold Applications.—While it is difficult to understand in what way the application of an ice-cap to the head can materially influence the physical condition of the brain or its circulation, and while it would seem that the amount of heat abstracted from the deeper tissues would soon be replaced by the warm blood-stream going to the brain after being heated by passing through other portions of the body, it is a clinical fact that in **inflammatory conditions within the cranium** the application of an ice-cap (or ice-water coil) to the head gives more relief than any other single measure. In almost all the **inflammatory affections of the throat** the application of an ice-bag, for which purpose special forms of the latter are made (see Volume IX), or of the narrow throat-coil, not only brings relief from the pain and discomfort, but seems to have some beneficial action in lessening the degree of inflammation and shortening its course Occasionally, however, it will be found that instead of producing relief, the external application of cold to the front of the neck causes an increase in discomfort, and this without any evident reason. In such cases it will almost invariably be found that relief can be obtained by going to the other extreme and using hot applications.

The use of external cold to the chest in **bronchitis** would seem rather to be counterindicated, and I know of no advocacy of its employment, although within recent years there has been a great deal said in favor of the application of an ice-bag or bags to the chest in the treatment of **pneumonia.** (See Volume IX, p. 522.) Some of the reports in regard to this use of the ice-bag are extremely favorable. It is, however, in many of them not mentioned whether the pneumonia was of the croupous or of the catarrhal form, or whether primary or secondary in origin. After a moderate use of the ice-bag in cases of croupous pneumonia I cannot say that I have seen any marked evidence of its either bringing relief to the patient or influencing the course of the disease in any way.

It has, however, been adopted entirely by many good observers, and its use is certainly worthy of trial. Theoretically, it has the advantage of abstracting heat from the body, and the parietal pleura is near enough to the point of application to be influenced directly by the lowering of temperature; it is also possible that the effect of the ice-bag upon the blood-vessels of the skin may diminish the caliber of those supplying the parietal pleura. It has been stated by some that the use of the ice-bag in pneumonia rather tends to increase the liability to pneumococcus empyema, probably by lowering the vitality of the pleural tissues. The point is difficult to determine. By some it is advised to apply the ice-bag to the abdomen in cases of pneumonia, not only for its antipyretic effect, but also because it is supposed to deepen the respiratory movements. [The editor prefers external heat to the ice-bag in pneumonia.]

In the treatment of **cardiac affections** the ice-bag has won a distinct place. In many cases of tachycardia the pulse-rate is distinctly lowered by the application of an ice-bag to the precordium. Whether because of this lowering of the cardiac activity or because of some influence upon the caliber of the internal mammary artery, the ice-bag has, to a great extent, superseded counterirritation by means of blisters or cupping in the treatment of **pericarditis.** The second explanation would not apply to its use in cases of **endocarditis,** because of the totally different source of the blood supply of the superficial structures overlying the heart and that of the endocardium; while in endocarditis involving the valves of the heart the effect on the vasomotor mechanism must be very slight, in view of the fact that the auriculoventricular valves only contain blood-vessels for a short distance from their attachment to the endocardium, and the semilunar valves contain no blood-vessels at all. In the absence of definite knowledge as to its exact mode of action it must be granted that the application of an ice-bag to the precordium in cases of pericarditis and endocarditis is of value, even though it be acknowledged that the effect of any form of local treatment in these conditions is extremely difficult to estimate. Other applications of the cold **precordial coil** are discussed in the volume on Hydrotherapy. [An ice-bag over the precordium is useful to restrain pulmonary hemorrhage.]

The value of the ice-bag in the treatment of **inflammatory conditions of the abdominal viscera** is generally recognized; but the aid of surgery is now systematically invoked so much earlier in the course of the disease that local applications to this portion of the body have ceased to play so important a rôle. Before the period arrives when surgical intervention is called for, or when surgical treatment is for any reason

unavailable, the ice-bag is by far the most valuable agent in the local treatment of inflammatory conditions within the abdomen. For example, in **appendicitis,** before the desirability of operation has been definitely determined, an ice-bag applied to the right iliac fossa seems not only to relieve the pain, but also to have some effect on the deep-seated morbid process. As in like conditions in other parts of the body, so here, the supposed result cannot be explained satisfactorily; and as the effect, if any, upon the vascular supply of the appendix must be to diminish the caliber of the blood-vessels, and the one nutrient artery of the appendix would therefore have its caliber diminished, the procedure would tend rather to increase than to diminish the ever-present danger of gangrene of the wall of that portion of the gut. For this reason, among others, those who advocate invariable operation in appendicitis condemn the use of the ice-bag.

Soothing Applications and Lotions.—The materials of various kinds which have been advised for the relief of local troubles beneath the surface are innumerable. A large number of these have been discarded as of no value except for their moisture. Of these, might be mentioned arnica and other similar preparations derived from the vegetable kingdom, which probably depend entirely for any beneficial action that they may have had upon the alcohol contained in them. One of the oldest of such applications is **lead-water and laudanum.** To which of its constituents this lotion owes its well-earned reputation is doubtful. It can hardly be supposed that the acetate of lead contained therein could be absorbed and have any action upon the parts beneath the subcutaneous connective tissue, as it would probably be at once taken up by the lymphatics of the skin, which have no communication with those of the joint for disease of which the application is made. The same might be said with regard to the opium contained in the mixture. As the remedy is usually applied under an impermeable covering, such as paraffin-paper or oiled silk, the alcohol and water can have no cooling action through evaporation. The only other property by which this application could exert its effect appears to be its moisture, in which case the action would be similar to that of a poultice; nevertheless, in spite of these theoretic considerations, there is no doubt that local applications of lead-water and laudanum to inflamed structures not too far below the surface are worthy of the high esteem in which they have been held for a very long time. In **arthritis** due to infection, whether rheumatic or of some other nature, lead-water and laudanum certainly brings relief.

Recently the employment of more specific local remedies for the

treatment of rheumatic arthritis has received considerable attention. From a fairly extensive clinical experience it can, I think, be asserted that in the **arthritis of acute articular rheumatism** and in that due to infections, both chronic and acute, the local application of **oil of wintergreen** is of advantage in relieving pain and diminishing swelling. It is usually applied by soaking a piece of patent lint in the oil, placing this over the joint, and covering it with an impermeable sheeting. Various preparations of **methyl salicylate** and allied synthetic drugs have also been used for the same purpose, and have an advantage over the oil of wintergreen in the matter of cleanliness. The material is usually painted over the inflamed joint, which is then covered with rubber tissue and a bandage. How much of the salicylic acid contained in these preparations actually reaches the joint cannot be determined—it is probably very small in amount. That the salicylic acid is absorbed from these preparations is shown by the fact that shortly after their application salicyluric acid can be demonstrated in the urine.

In this class belong also the various preparations of **clay and glycerin,** with, possibly, some sedative drug, of which several are on the market under various trade names. They owe such therapeutic value as they possess to their close kinship with the old-fashioned flaxseed poultice, and have little advantage over its modern descendant, the antiseptic poultice or heating compress; but, representing as they do a visible, palpable body, they will also enjoy a certain vogue, like the time-honored "kidney plaster," which affords so infinite an amount of comfort to patients of certain type.* [There is also some mechanical advantage in the elastic compression exerted by the clay when skilfully prepared and applied; in certain cases its capacity to absorb moisture and thus keep the underlying surface dry is of benefit; and in burns, ulcers, and the like, the exclusion of air is also therapeutically useful.]

LOCAL BLEEDING

Local bleeding is being more and more abandoned as a method of treatment. To some extent this is due to the fact that its use in many cases was based upon an erroneous etiology. It is possible that the pendulum may have swung too far in the other direction, and that local bleeding might be of benefit in some conditions in which, at the present

* For a more comprehensive account of hot and cold applications to the body and other subjects touched upon in this chapter the reader is referred to Volume IX, Part I, Chapters I (pp. 17–26) and IV (pp. 46–48), and Supplemental Chapters, Chapters III and IV (pp. 242–278).

time, it has ceased to be regarded with favor. While it is now known that the condition of the blood-vessels at an inflamed point is merely secondary to the etiologic factor and its results, yet there is no doubt that in many cases much, if not all, of the pain present in inflammatory conditions is due to vascular overdistention. By temporarily diminishing the contents of these overfilled vessels we may at least, in a large measure, relieve the pain, and it is difficult to see how the partial emptying of these blood-vessels can have any unfavorable effect upon nature's attempts at repair or protection. In **periosteitis,** especially in the region of the mastoid process, the effects of local abstraction of blood are prompt and striking. In **iritis** the application of a leech to the temple changes the whole picture of the case. In **pleurisy** the application of a leech over the painful point usually gives prompt relief, although in this instance it is more difficult to understand the exact mode of operation. In **congestive conditions within the cranium** leeches to the temples or behind the mastoid processes are often beneficial. In **orchitis** leeches are sometimes applied with good effect to the scrotum.

Wet-cups.—Wet-cups are no longer used as a means of diminishing blood-pressure, or the total quantity of blood or any of its constituents, except—and then unsatisfactorily—when consent cannot be obtained for venesection. The wet-cup is occasionally used for the local removal of blood from a painful area of the chest in **pleurisy** or **pneumonia,** although its use for this purpose is steadily declining. Wet-cupping over the kidney is employed in some cases of **uremia** or of **renal failure** without uremic symptoms. In abdominal conditions local bleeding is now entirely abandoned, and rightly so. Many pathologic conditions within the abdomen are due to infection and sooner or later require surgical relief; hence it is a well-recognized rule of practice never to apply leeches or cups to the abdominal wall, even though they may possibly in the past have been found to relieve pain, because they might complicate a possible surgical operation. The extent to which a leech applied to the abdominal wall may be productive of harm was well illustrated some years ago in a patient with appendicitis whom I saw in consultation with a physician who had applied two or three leeches to the right iliac fossa. Within the next few days operation was urgently demanded, and on incising the abdominal wall, blood was found extravasated between all the layers to the peritoneum. The extravasation and suppuration of the structures of the abdominal wall greatly interfered with the healing of the wound and prolonged the period of convalescence.

Leeches.—Leeches are useful chiefly when the available area is too

small for the application of a cup or the surface is so irregular that a vacuum cannot be produced. Instances of the former condition are found in the temporal region, the angle of the jaw, and the mastoid; while in those having but a small amount of subcutaneous fat the application of wet-cups to the chest may be impossible, owing to the projection of the ribs beyond the interspaces. In most of the large cities the application of leeches is undertaken by professional cuppers and leechers. The use of leeches is, however, by no means a difficult matter, although sometimes requiring a considerable amount of patience.

Application.—The easiest way to apply a leech is to place it within a test-tube, the closed end of which has been broken off, applying the smooth mouth of the tube to the point desired, and then, with a lead-pencil, gently pushing the leech down until it touches the skin. Sometimes, even with the greatest exertion of patience and ingenuity, the leech will fail to bite. In any case the skin should have been thoroughly washed with soap and water and further cleansed with alcohol, in order to prevent danger of septic infection of the wound, and also because the leech seems to be very much more willing to bite a clean skin than one on which secretions have collected. It is said that the placing of a drop of milk on the skin will cause the leech to bite; an easier method is to puncture the patient's finger or the lobe of the ear, and place a small drop of blood on the point where the leech is to take hold, an expedient which usually proves successful. When the leech has become filled with blood, it drops off of its own accord. If, however, it is desired to remove the leech before it is completely satisfied, this can be accomplished by immersing the body of the leech in strong brine. Leeching should never be employed at a time when it will not be possible to have the patient watched, in order to prevent too great a loss of blood after the leech has dropped off. This is, of course, especially true in the case of children and old people. The amount of blood that can escape after the removal of a leech is surprising. At times, owing to the triangular shape of the leech-bite, the bleeding is too free and must be controlled. This can usually be accomplished perfectly by light pressure with a gauze pad and rubber plaster or a bandage. In case this should fail, a solution of suprarenalin may be painted freely on the wound. It is said at times to be necessary to use a transfixion pin and a figure-of-eight ligature, and such extreme measures may possibly be required when direct pressure against some underlying resisting structure is not possible.

The means by which the local abstraction of blood is effected seems to have little if any influence on the results obtained. The leech and

the wet-cup both leave marks that never disappear, although the leech-scar is so much the smaller that the leech should be preferred when the question of disfigurement is a factor.

VENESECTION

In considering any method of treatment it is well for us to see what analogies nature presents corresponding to the artificial means to be employed. In connection with the question of venesection we have some guide in natural processes observed in certain morbid conditions. The best illustration of this is the epistaxis that frequently occurs in those who have for a long time been eating and drinking to excess. The frequent hemorrhage from the nose occurring in cases of heart disease, especially in the young, is another instance having a bearing upon this subject. So, also, the rupture of distended hemorrhoidal veins, bleeding from which is often followed by relief of distressing symptoms, might be cited, as well as the disagreeable results sometimes seen to follow the cessation of a hemorrhage from these vessels. While bleeding has fallen into disrepute, there is no doubt that it is of value in a certain small number of conditions. The folly of the old practice of copious periodic bleedings in health and upon the occurrence of almost any evidence of disease is no argument against judicious bleeding when true indications for it exist. In our endeavor to 'prove all things' we are in some danger of forgetting the other part of the saying, 'hold fast to that which is good.'

General Indications.—Five objects may possibly be obtained by the withdrawal of blood from the general circulation. In the first place, any **poisonous material,** such as toxins, with which the blood may be charged, might be sufficiently diminished to lessen appreciably the danger to life or health. Second, the total **quantity of blood** in the circulation can readily be reduced by the withdrawal of a certain proportion of it from the superficial veins. Third, by bleeding and the subsequent infusion of therapeutic saline solution the **composition of the blood** can readily be changed in many cases in which the blood may be described, for want of a better term, as concentrated. Fourth, the quantity of blood going to a certain **portion of the body** may be lessened by opening a vein. Fifth, the **condition of the circulation** to the distal side can presumably be altered by allowing a steady flow of blood to take place through the vein therefrom, so causing a freer emptying of the venous radicles, capillaries and arterioles of the part.

The quantity of blood that can be lost without jeopardy to life

probably varies somewhat in different animals. Fredericq found that in dogs recovery easily occurred after a loss of blood amounting to 2 or 3 per cent. of the body-weight, whereas the loss of 4.5 per cent., or more than one-half the total bulk of the blood in the body, was usually followed by death. While, for obvious reasons, it is not definitely known to how great an extent the human being can lose blood and still recover, the estimate of 3 per cent. of the body-weight may be considered as approximately correct, although probably a greater amount of blood can be spared when transfusion or saline infusion is practised.

Removal of Poisons

Uremia.—The best example of systemic poisoning in which bleeding may be indicated is **uremia.** While it would seem that a comparatively small amount of poison could be removed with the blood obtained by venesection, there is no other way by which we can hope so promptly to diminish, at least to some extent, the quantity of the poison circulating in the body. When the dose of poison is overwhelming, the quantity removed with the blood obtained by venesection is, of course, not large in proportion to that remaining behind; nevertheless, it is to be borne in mind that, ordinarily, a case of marked uremia is seen when the accumulation of poisonous materials within the body is just sufficient to cause dangerous symptoms, and that the blood removed by venesection may reduce the total quantity to within safe limits; giving time, therefore, for other measures to be employed to rid the body of a larger quantity of the poison. In uremia vascular tension is, as a rule, tremendously increased, and the lowering of tension by the withdrawal of a certain amount of blood from the circulation may be considered beneficial, even though we know that after a time vasomotor contraction and a return of the pressure to the normal take place in animals bled for experimental purposes. In uremia tension is elevated beyond the normal point; hence it is fair to presume that the same mechanism which causes the secondary arterial contraction in the case of a healthy animal submitted to bleeding is not brought into play, because the removal of blood simply brings the tension down to the normal level and does not, therefore, give rise to stimulation of the vasomotor centers, as when tension is abnormally reduced in the experiments on animals. Practically, it is found that venesection is one of the most valuable means at our command for immediately obviating the harmful effects of that retention of excrementitious material of, at present, unknown nature, to which the term uremia is applied. In no other way can we so quickly terminate a uremic convulsion or cause the disappearance of

uremic coma. In addition to these beneficial effects, the removal of a suitable quantity of blood seems to be of assistance to the heart in performing its labors, which are always increased by the renal disease in the first place and, in the second place, by some of the uremic manifestations, notably, convulsive movements.

No rule can be given as regards the **quantity** of blood that should be withdrawn in uremia. But little benefit can be expected to follow the withdrawal of less than ten ounces; as a rule, the removal of a pint is necessary to obtain the best effect. In **puerperal eclampsia** the value of removing a much larger quantity than that mentioned is proved by a vast mass of testimony. [Wallace's rule to "bleed enough" applies.]

Indications almost precisely similar to those present in uremia may exist in **acute lead-poisoning,** and may also be met by venesection. It is one of the best and promptest means of relieving acute saturnine mania and the distressing headache that is usually present at the same time. It may be employed with benefit in any severe case of lead-poisoning that is seen early. The chief object being to remove as much of the poison as possible from the circulation, the blood-letting should be free,—from sixteen to twenty ounces being withdrawn,—and should be followed immediately by saline infusion. If secondary anemia is already well established, venesection must, of course, be practised with caution and may be counterindicated by the general condition.

[In **croupous pneumonia,** venesection, together with saline infusion, is useful at times to reduce the toxemia, apart from the relief given to the circulation, as discussed in a later paragraph of this article. The circumstances of individual cases differ so much that no exact rule can be laid down for this measure. In young robust patients with the form of disease termed "sthenic," it may be done early. In others there should exist some definite indication, as in delirium, threatening cardiac failure, suppression of urine, or other sufficient symptom; and in deciding upon it, age and all other factors must be considered carefully. In **acute alcoholism,** and especially in **delirium tremens,** the editor has observed immediate and lasting benefit from venesection coincident with saline venefusion. Packard had good results in **sunstroke** and **heat-exhaustion.**]

Diminution of Quantity of Blood in General Circulation.—The existence of true **plethora**—that is, an increase in the total volume of the blood—cannot be considered as proved, although arguments against it derived from examination of the blood taken from the finger-tip cannot be looked upon as conclusive, inasmuch as the various instruments employed in such examinations merely enable us to determine

the relative proportions of hemoglobin, corpuscles, and serum in a given quantity of blood. We have at present no proof of the existence or nonexistence of an actual increase of the total quantity of blood within the body. In olden times, when regular vernal bleedings were practised, this question was one needing solution. At the present time, so far as venesection is concerned, the existence or nonexistence of an actual plethora is of but little importance. We know that by preventive measures, such as diet and exercise, the condition for which vernal bleeding was formerly practised can be prevented; while measures other than bleeding can be employed to obviate the bad results ensuing from overfeeding and lack of exercise, for which the letting of blood was at one time considered essential.

Rapid reduction of the total mass of blood in active circulation is, nevertheless, an important factor under certain conditions. The most important of these—in fact, the only one for which bleeding is now practised to any extent—is **cerebral hemorrhage.** In endeavoring to prevent the pouring-out of more blood into the cerebral substance one of the most valuable means would naturally be the removal from the blood-vessels of a certain amount of their contents, thereby diminishing vascular tension and allowing the rent in the vessel that has ruptured to become closed by a clot. In no other way can we so quickly lower arterial tension without at the same time stimulating the heart or producing other results that are undesirable.

The amount to be withdrawn varies somewhat with the condition of the individual and the gravity of the hemorrhage into the brain. The withdrawal of eight ounces of blood from the arm may possibly accomplish the desired result, yet usually it is better to remove sixteen ounces or more. It is of prime importance clearly to establish the diagnosis of cerebral hemorrhage before resorting to bleeding, as in the case of cerebral embolism removal of the blood from the arm could do no good, and in the case of thrombosis of the cerebral vessels the withdrawal of blood would do actual harm.

[Venesection, quite free at times, and if necessary supplemented by the administration of aconite, may also be resorted to in the endeavor to **avert** threatening cerebral, and perhaps pulmonary, hemorrhage.]

Alteration of Composition of the Blood.—Increased concentration of the blood is never seen except in **cholera,** and possibly in **insolation** [and in certain cases of **uremia**]. In cholera, bleeding could only be productive of harm, and the injection of normal saline solution into the veins, beneath the skin or high up into the bowel is the best means at our command for obviating the effects of loss of the fluid constituents of

the blood. In insolation [and often in uremia], blood taken from the arm looks and feels viscous and thick. No facts are at hand to show whether this condition of the blood can be obviated by saline infusion alone; but, as I have elsewhere mentioned, the results of bleeding followed by saline infusion in these cases may be extremely gratifying.

Diminution of Quantity of Blood Going to Certain Portions of the Body.—In the fourth category we have some of the conditions most certainly relieved by the letting of blood. When the work of the right ventricle is hindered by obstruction in either the pulmonary circuit or in the left side of the heart, distention of the wall may occur to an extent sufficient to abolish ventricular contraction. This is seen especially in **mitral valvular disease** or in **dilatation of the mitral orifice,** in **pulmonary emphysema,** and in **croupous pneumonia.** In all these conditions there may come a time when the embarrassment of the right ventricle and auricle is shown by an accumulation of blood in the venous system and distention of all the superficial veins. For a long time this was looked upon as being an absolute indication for the removal of blood from the arm; lately even this indication for bleeding has been called into question. One of the chief arguments used by those opposed to blood-letting under the conditions mentioned is that it is impossible to empty the right auricle or ventricle through bleeding, owing to the presence of valves in the veins. Doubtless the contention is true that the blood removed from the arm in bleeding from the median basilic vein is not directly derived from the heart; if, however, the right ventricle and auricle are capable of contraction, and some of the blood going to them is removed by opening one of the large venous trunks not very far removed from the orifice opening into them, it is, I take it, conceivable that potentially we lessen the amount of blood in the right auricle by removing some of the blood which would shortly be poured into it. Practically, the letting of from twelve to sixteen ounces of blood from the median basilic vein in certain cases of **failure of the right heart** with overdistention of the superficial veins gives prompt and more or less lasting relief to the patient, and removes some of the dangers present. Such embarrassment of the right heart is frequently seen among hospital patients suffering from mitral diseases or emphysema and chronic bronchitis, and occasionally in the course of croupous pneumonia, especially in those whose heart-muscle has previously undergone degenerative changes. Whether the bleeding in these cases acts by directly lessening the quantity of blood going to the right auricle or by lessening the total amount of blood within the blood-vessels, is difficult to say and is not susceptible of proof. Certain it is, however, that the conditions may

be rapidly changed, so that within a few minutes after bleeding has commenced orthopnea may cease, cyanosis disappear, and the heart act with greater vigor and regularity. In these cases there is a tendency for the blood to accumulate in the venous portion of the circulation. If the whole venous system becomes overdistended, it is reasonable to believe that the arteries contain less than their normal amount of blood, and that the left ventricle receives during each diastole, and expels during each systole, less blood than would be the case were the distribution of arterial and venous blood nearer the normal standard. Under these circumstances the arterial pulse may be small or even imperceptible; and the increase in the volume and force of the arterial pulse is one of the results that frequently follow the abstraction of blood from the arm. This result of bleeding, however, is probably due to the lessening of embarrassment of the action of the right auricle and ventricle, rather than to any other cause, and the fact is mentioned here only in order to point out that a strong, full pulse, which was at one time considered an indication for the letting of blood, may be absent in those in whom the overfilling of the venous system most urgently calls for venesection. The amount of blood to be withdrawn cannot be definitely stated, but it will usually be found that after the escape of from eight to ten ounces of blood the patient looks and expresses himself as feeling decidedly better. While the results of percussion in outlining the area of cardiac dulness cannot be strictly relied upon, as has been frequently pointed out recently in connection with certain papers upon the Schott method of treating heart disease, in a number of cases I have convinced myself that the right edge of the cardiac dulness has distinctly advanced to the left after a free bleeding from the median basilic vein. In some cases this diminution of extension of cardiac dulness to the right has amounted to as much as one centimeter.

Venesection is now never employed for the purpose of emptying a part distal to the point of bleeding.

Technic.—The operation of venesection is so well known that it would seem superfluous to describe it, were it not for the fact that the technic of the procedure is absent from many of the best text-books of the present day. The only vein that is at the present time selected for the withdrawal of blood is the median basilic. Absolute cleanliness must be observed with regard to the operator's hands, the instruments employed, and the skin covering the vein to be incised. Careful and prolonged scrubbing of the hands with soap and water, followed by a free bath with alcohol and then a solution of corrosive sublimate, 1 : 1000, should be employed. The instruments to be used should

be carefully sterilized by boiling for fifteen or twenty minutes. In order to increase the fulness of the vein and at the same time prevent the danger of entrance of air when the vessel is opened, compression above the elbow is employed. Manifestly, to obtain the best results our object in applying the bandage should be to compress the venous trunks without obstructing the flow through the arteries. For this purpose a bandage of unbleached muslin or gauze, bound tightly around the arm, is usually sufficient, although the use of a portion of the bandage in the form of a pad over the large venous trunks may be necessary in some cases. This is especially true in the class of cases discussed above, in which venous distention is not a prominent feature—as, for example, in uremia. The bandage having been properly adjusted and the antiseptic precautions having been observed, two plans are open to us: either to make an incision directly into the vein or to cut carefully through the overlying tissues until the wall of the vein is reached. The first of these proceedings is so much more quickly accomplished and gives rise to so little pain, that when the veins are sufficiently prominent, it should be employed. Owing to the danger of injuring the brachial artery it is well that the incision should be made from the lateral, rather than from the anterior, aspect of the arm. For thus opening the vein at one stroke the best instrument is a sharp-pointed, curved bistoury. If it is sharp, the operation is almost painless and the wound made is sufficiently wide to allow of the free outflow of blood. When more careful dissection down to the vein is made, the ordinary scalpel is a more desirable instrument. When the venous distention is very great, the blood sometimes escapes with such a rush as soon as the vein is punctured that everything in the neighborhood of the patient is spattered with blood, unless a folded towel has been laid in front of the vein as close as possible without interfering with the work of the operator. When venous distention is not marked, the flow of blood may have to be encouraged. This may be accomplished by having the patient grasp some solid object and alternately tighten and relax his hold upon it. The amount of blood which is caused to flow by each contraction of the muscles of the forearm is quite remarkable.

After a sufficient quantity of blood has been withdrawn, the fillet surrounding the upper arm should be cut through, a compress of sterile lint pressed over the skin incision, and a rather firm figure-of-eight bandage applied. [Sometimes, especially in difficult dissections, it is necessary to lift the vein on a metal instrument, noose it above and below the predetermined point of opening, and tighten the ligatures after the bleeding has been sufficient. A triangular nick with small-pointed

scissors is usually the best incision in such a case.] If the incision is a long one, as when dissection has been necessary to expose the vein, one or two sutures should be applied in order to cause the wound to heal quickly. When the vein has been simply punctured through the skin, this is usually not necessary. The dressing can be left on for three or four days unless the surface exposed to the air becomes stained with discharge. When at the end of that time the dressing is removed, the wound in the skin is usually found completely healed, providing thorough cleanliness has been observed in the preparation of the skin, the instruments used, the operator's hands, and the dressing applied after the operation is completed. Considerable stress has been laid upon the danger of air entering the vein. While it is, of course, to be guarded against, the danger from this source in bleeding from the median basilic vein is so slight that practically it can be ignored.

AN OUTLINE OF THE PRINCIPLES OF THERAPEUTICS WITH ESPECIAL REFERENCE TO PHYSIOLOGIC THERAPEUTICS

BY

SOLOMON SOLIS COHEN

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Measures of scientific therapeusis are not few; but a comprehensive science of therapeutics does not exist. The reason is not far to seek: physiology, pharmacology and pathology—and, back of these, physics and chemistry—have not yet solved the problems whose solutions are the needed bases for therapeutic science. Hopeful outlooks, however, are opening in one direction through the recognition that medicine, including therapeutics, is a branch of biology, and is to be studied as such; in another, through those brilliant researches that daily continue to add many important facts and not a few principles to our knowledge of vital reaction. Not the least important of such researches are those throwing light upon the interrelations of vital with physical and chemical processes. These give promise, probably for the first time in medical history, of the establishment of fundamental data from which general therapeutic laws may be induced; to give scope in turn for scientific deductions and practical applications. Even now, apart from the direct advances in practice that have resulted from studies in the biologic and chemical laboratories,—as in the varied uses of internal secretions, of antitoxins and of solutions of definite molecular concentration and ionic constitution,—our general attitude toward questions of disease and recovery has been powerfully influenced and our general course in the management of the sick modified for good.

Thus far, nevertheless, contemporaneous therapeutic advances, both direct and indirect, have been, like those of former days, advances in art chiefly. Indeed, did not therapeutic art now, as ever, outrun medical science in general, physicians would grievously fail in their daily work; for therapeutics is, and must be, essentially utilitarian. Its generally recognized **objects**—more readily formulated from the viewpoint of art than from the viewpoint of science—are the preservation and the restoration of health. The **preservation of health** includes,

but transcends, the negative aim of the *prevention of disease;* and the **restoration of health,** implying the existence of disease, includes the *prolongation of life* and the *promotion of comfort*—which, as palliative aims, may, indeed, become the final ends of therapeutic intervention when it is seen that complete recovery cannot be achieved.

It is not to be too hastily assumed, however, that the practice of therapeutics is but haphazard guess-work or blind routine. Observation continued and recorded over the centuries has established a body of therapeutic principles, empiric and inferential, admittedly insufficient to constitute an exact science, yet fully warranting the title of scientific art. This art, indeed, embodies in its rules many scientific laws, in its practice many applications of scientific inductions; nor is it wanting in great generalizations. It is, however, deficient in the knowledge necessary to coördinate its generalizations with its practice and is dependent for advances in such knowledge upon discoveries to be made in other sciences.

The Cardinal Therapeutic Principle: Recovery is a Biologic Adaptation

Examining the question from the viewpoint of medical history, it is seen that one **cardinal principle** virtually underlies all therapeutic measures—even the most fantastic. It is the function of the student of therapeutics to make this principle clear, so that, being ever in the consciousness of the physician, he shall not practically deny and oppose, even while tacitly assuming, it. Most therapeutic errors have arisen out of such contradiction between act and thought. Whatever the method by which the restoration of a sick person to health has been sought,—whether the incantations of a sorcerer or the mystic influence of a faith-healer, the attenuations and dynamizations of homeopathy or the bold manipulations of osteopathy, dosage with domestic simples or the administration of the elegant preparations of modern pharmacy, the electric and hydriatric applications of the charlatan or those of the scientific physician,—whether the measures practised have been rational or irrational, well or ill chosen, helpful or harmful,—beneath each and all lies the assumption that, given favorable conditions, the human body suffering with disease can, and will, return to health. The ultimate object of every therapeutic procedure is thus the same: the induction of the conditions favorable to this return. Differences arise not only in the choice of measures—which, being a matter of detail, is necessarily subject to change with new discoveries—but also in the manner of viewing the restoration aimed at—which, depending on a funda-

mental fact of existence, is not subject to change. The common view seeks its impulsion without; the enlightened view sees it arise within. The common view terms the process "cure," and assumes the cure to be the direct result of the treatment adopted. It may be able to trace no relation of necessity between treatment and cure—often, indeed, attributing remedial virtue to measures that are, at best, without influence; and its lack of analysis of either recuperative or therapeutic processes readily leads to the adoption of measures that may retard or even prevent the return to health. The enlightened view terms the process "recovery," and recognizes that the inherent powers of the organism have brought the recovery to pass. It thus sets up a guide or standard of treatment in the natural recuperative processes, and, placing the influence of therapeutic measures in a new light, subjects that influence to a more critical analysis.

This view has not waited for our time to give it recognition and formal statement. Hahnemann need not have combated it so violently had it not been frequently upon the lips of his cotemporaries—the irony of that controversy being that Hahnemann and his followers, with their inert dilutions and attenuations, virtually trusted in, and helped to demonstrate the efficiency of, the natural healing power that they denied; while, in too many instances, their opponents, with heroically unwise treatment, practically recanted the faith professed. Hippocrates, in pointing out that the true function of the physician is to aid "the patient in combating the disease," says that he must be "the servant of nature"; and this doctrine has been echoed and reëchoed in varying phrase by all the great teachers of medicine who have left us the record of their thought. It may thus be restated in the language of the day:

Recovery from disease, both in its perfections and in its imperfections, is but one of the manifestations of the vital adaptability underlying organic evolution, and is subject to the laws of biologic adaptation in general.

When this fundamental truth informs and dominates not only the mental attitude of individual physicians, but the authoritative teaching of medical schools, the first great step toward the institution of a definite science of therapeutics will have been taken. It will then be recognized by all pupils of such schools that before considering the question of treatment at all, it is necessary to analyze every individual case of disease in such a way as to make as clear as possible certain fundamental factors of the situation. These are in brief:

The exact character of the departure from health; its causation; the stages through which it has passed; the further stages through which it may or must pass in the absence of intervention; the morbid and

salutary (destructive and reconstructive) elements in each of these stages; the modifications that are possible in present and future stages; the possible terminations and their determining factors. This analysis we term, as a whole, the diagnosis (and prognosis); and its branches may be called respectively the *clinical*, the *etiologic* and the *pathologic* diagnosis. Each of these branches may be quite complex, and any or all of them obscure, the diagnosis as a whole thus being rendered more or less imperfect.

The Hippocratic Principle in Applied Therapeutics: Do Good or Do No Harm

In so far as the imperfection of diagnosis affects matters of practical importance it necessarily hampers the treatment, rendering the latter empiric rather than rational. When imperfection and obscurity are so great that no clear idea of what is desirable in the way of treatment can be obtained, it is obviously the part of wisdom to refrain from interference. Thus the Hippocratic maxim, "*to do good or do no harm*," may still be accepted by the most advanced modern physician as the **first principle of applied therapeutics.**

One of the special applications of this principle may here be pointed out—partly because it will scarcely find place in our later discussions; partly because it needs definite and early statement, so that it may be kept in the background of consciousness as a qualification of all that may be said concerning the methods and means of aiding the organism in its struggle for continued and unimpaired existence: *The physician must do his best to save life and to avert damage to the organism ; but he is not called upon to add to the misery of impaired life by futile efforts at its improvement, or uselessly to prolong or increase the agony of death.*

THE THERAPEUTIC DIAGNOSIS

Assuming that the diagnosis in its various branches thus far considered has been made, the next step is along the same line. The **therapeutic diagnosis** is to be considered.

The **elements of the therapeutic diagnosis** are many, and can here be given only in outline. In any study the cardinal principle already set forth must be kept in mind—namely, that recovery from disease is a manifestation of the inherent powers of the organism and not due to extraneous forces. It is, in essence, merely an apparent exaggeration of the constant adjustment (reaction, interaction) between organism and environment, between one part of the organism and

another, between the organism as a whole and its various parts, through which life is manifested and health is maintained. Morbific agents destroy, or alter the action of, some part or parts of the organism: reacting against the consequent disturbance (*resisting it*), the organism, by virtue of its *vital adaptability*, modifies the action of other parts and its action as a whole, in a way that tends to **protect** itself from further injury; to **expel, destroy, neutralize,** or **antagonize** the offending agent; to **counteract** the ill effects of the morbid disturbances; and thus to **restore** the former harmony of function (*vital equilibrium*) constituting health. Were resistance perfect, morbid disturbances would be unknown; were defensive adaptation complete, disease would be of short duration and recovery take place spontaneously. Such phenomena as those of *natural immunity* show that to various potentially inimical agents, many animals and, in some instances, men, ordinarily offer perfect resistance; but this resistance may become weakened or broken down, and then the attack of the pathogenetic factor will result in disease. Moreover, to a great variety of hostile agents men offer imperfect resistance, and against the effects of these agents oppose an incomplete defensive adaptation. The imperfection may consist in delay; in want of appropriateness; in deficiency or excess of extent or degree or force; in deleterious associations—as when reactions favorable to the organism as a whole involve damage to parts, or reactions favorable to parts involve dangers to the organism as a whole. Given time, nature may be competent to seal by spontaneous clotting a wounded vessel; in capillary hemorrhage it may be safe to wait for such clotting, or to assist it merely by pressure; in wounds of sizable arteries the surgeon resorts to the hemostat, the cautery, or the ligature. Elevation of temperature is to be considered a protective response in cases of intoxication by the products of the pneumococcus, but heat-production proceeding to a degree beyond that necessary to neutralize the toxic properties of the microbe—hyperpyrexia—may in itself become a danger. An organ enlarged to carry on function despite morbid alterations may do so at the expense of neighboring tissues or of the organism as a whole. Tumor formations of various kinds may become developed in response to external irritation as an exaggeration of a normal protective process. Adhesions may take place between inflamed structures, as in the joints, the pleura, the appendix and the intestines; the fundamental processes leading to such conditions are, indeed, the same factors that give to the organism its power of defense, but disadvantage results from the time or place or degree of the special manifestation. Thus the tendency to form fibrous adhesions in the neighborhood of the appendix sometimes

saves life by barring the entrance of pus into the general peritoneal cavity; yet the same process may cause considerable pain and distress, and even threaten life, by producing distortions and difficulties of movement among the intestinal coils.

Art, therefore, must be called upon to aid, supplement, and control nature, and thus the vocation of the physician arises. In Bigelow's expressive phrase, he has to "safe-conduct the patient" through disease to recovery. He must, however, be guided in his action by the character and direction of the natural defensive reactions and adaptations in the special case, and by his knowledge of defensive reactions and adaptations in general.

Factors Governing Intervention.—The first step to be taken in the therapeutic diagnosis is often the most difficult. The evidences of departure from health consist of alterations in the sensations of the patient and in the structure and functions of the body (in so far as these are discernible by the senses of the physician, aided, it may be, by instruments of precision); in other words, of signs and symptoms. Some of these alterations are morbid, that is to say, they tend to the impairment and destruction of life—they constitute disease. For an example we may cite the signs indicative of perforation in typhoid fever. These call for opposition. Others, however, are reactive, salutary; they tend to the preservation and perfection of life—they constitute natural efforts toward recovery. A good illustration is afforded by the pyrexia of certain infections, *e. g.*, acute lobar pneumonia, which, when within due bounds, is now generally admitted to be an element of favorable prognosis. These are not to be interfered with. Other phenomena involve both destructive and reparative elements, and, according as one or the other predominates, may call for therapeutic intervention or for "hands off!" The first step in the therapeutic diagnosis is to separate these classes of phenomena—a **qualitative estimate** of symptoms. But reactions salutary in kind may, as we have seen, be excessive or deficient, or may exhibit disproportion in degree or maladjustment in time to other factors in the natural defense or adaptation. Such excess, deficiency, disproportion, maladjustment, may call for stimulation or repression, supplementation, regulation, or control—the **quantitative estimate** is thus the next to be made.

Let us take examples. Cardiac hypertrophy in compensation of valvular lesions is one of the best illustrations of restorative adaptation. That it may be deficient, or having been efficient become ruptured, is a commonplace of medical teaching. Not so much emphasized is the opposite fact, that, often, and especially in cases of mitral stenosis,

it becomes excessive because the mechanical conditions are such as to prevent the general circulation from attaining a corresponding uplift. The adaptation is *disproportionate;* its excess must be restrained.

The skin may attempt to take on a vicarious eliminative function in cases of renal failure, but the natural sweating be too scanty or irregular to be effective. Adaptation is *deficient;* stimulation is called for.

Cough is a natural means of expelling harmful substances from the air-passages, but may be a source of useless distress when bronchial secretions are too scanty or too viscid for ready expectoration. Defensive reaction is *maladjusted in time;* the premature factor is to be restrained, the tardy factor stimulated—"paregoric and squill" has justification. Diarrhea serves the purpose of removing irritating matters from the intestine, but it may take the form of small and frequent stools, ineffective and exhausting. The *irregular* defensive reaction needs *supplement* and *control;* irrigation or a cleansing dose of calomel or castor oil, followed by an opiate to check peristalsis, may be the best treatment.

It is thus evident that through an analysis of symptoms, qualitative and quantitative, the physician arrives at his most momentous decision: to **intervene** or to **refrain** from intervention. The decision to intervene involves and includes a determination of the **purpose** of intervention.

In choosing the **direction** and **means** of intervention, however, other matters must be considered. We have already seen that neither the preservation nor the restoration of health is effected directly by the measures of the therapeutist. Health is a state of living organisms, and is preserved, or when impaired may be restored, only by the natural powers of the organism itself. All that the sanitarian or the physician may helpfully do is so to order the environment or so to alter the relations of the organism to the environment or of the parts of the organism to one another, as to bring about conditions favorable for the exercise of these natural conservative and recuperative powers. This applies even to instances seemingly contradictory of it, as the destruction and expulsion of intestinal parasites, or the ligation of an artery to control hemorrhage. Removal of the parasite excludes its further influence in provoking disorders, but the return to health would not follow in the absence of a restorative power in the organism. Ligation brings together the arterial coats, mechanically occluding the channel and preventing further blood-loss; but the processes that follow, making the occlusion permanent and establishing collateral circulation, are vital adaptations.

It is further to be borne in mind that the power to alter favorably

implies an equal power to alter unfavorably; hence attempts to alter conditions not understood may be the reverse of helpful. Or, again, the means employed to alter certain conditions apparently unfavorable may of themselves introduce new dangers, directly and indirectly. Thus antipyretic medication by means of the coal-tar products does indeed reduce febrile temperature; but apart from the fact that this is not always necessary,—and sometimes hinders the natural evolution of the combined morbid-recuperative process,—it is accomplished at the expense of the vital energy. The agents are distinctly depressing, especially to the heart, and death may be the result of the addition of drug-toxemia to the typhoid, pneumococcus, or influenza toxemia. So, too, the synthetic "headache powders" and "sleeping powders" recently so much in vogue are depressing to the organism as a whole and to the heart in particular, and may so injure the person who habitually resorts to them, that he fails to react properly in the presence of some acute infection. Though during the progress of the acute disease they be not given at all, prolonged illness, danger, even death may result because of their previous use.

Conclusion: Restatement of the Hippocratic Principle.—In considering the direct bearing of the foregoing considerations upon the management of the sick we recognize in disease—that is to say, in the morbid-recuperative process—three main possibilities:

1. The natural conservative and recuperative powers are perfect and sufficient and intervention is unnecessary.

2. The natural conservative and recuperative powers are sufficient ultimately, but recovery may be hastened and distress prevented or mitigated by intervention.

3. The natural conservative and recuperative powers are imperfect or insufficient and (*a*) intervention is desirable to promote comfort, hasten and ensure recovery, prevent accident and avert or minimize injury; or (*b*) intervention can nevertheless have no definite purpose, is useless, and may be harmful.

The question, however, is rarely presented in such clear-cut fashion at the bedside. Especially in acute affections, but also in chronic disorders, morbid and recuperative phenomena may be associated in puzzling combinations that render the decision difficult in the extreme. Knowledge of etiology and pathology, added to clinical experience, is our help and safeguard.

In summary, and somewhat in anticipation, I may be permitted to restate the Hippocratic principle in modern phrase, and with somewhat greater elaboration than the master's:

Intervention should be undertaken only—

(a) *when it is clearly seen to be necessary or desirable;*

(b) *when it can have a definite object* [or has a well-attested empiric usefulness];

(c) *when suitable means are available;* and

(d) *when the secondary or collateral or associated results to be anticipated either from the attainment of the immediate object, or from the nature and action of the means employed, do not constitute new dangers of equal or greater moment than those against which intervention is directed.*

Etiologic-Therapeutic Diagnosis

Our general diagnosis was (1) clinical or syndromatic, (2) etiologic, (3) pathologic. Our therapeutic diagnosis having by an analysis of symptoms become a determination to intervene for a definite purpose, must, in the absence of urgent symptomatic indications, leave symptoms for the moment and turn to etiology.

It is obvious that if a given chain of phenomena depends upon a known cause, and upon its present action, such phenomena can be terminated most readily by removing or opposing that cause. The first step, therefore, toward determination of the direction and method of therapeutic intervention is a study of etiologic factors. In Volume V of this series the nature and the causation of disease were studied in order to learn the best means of prevention. We recognized two main divisions of causative factors: **extrinsic** and **intrinsic;** from another viewpoint, *predisposing conditions* (falling chiefly, but not exclusively, into the latter class), and *exciting agents* (falling chiefly, but not exclusively, into the former class). We recognized, moreover, that the action of etiologic agents was not to introduce new qualities or powers into the organism, but merely to *modify* its habitual action or *evoke* its latent potentialities. In other words, that disease and recovery are alike vital processes, in which the organism itself is the most important factor.

The principles and methods applicable in prevention apply equally in treatment, and are founded on the natural defense and adaptation. We may **avoid protect from, remove** (*expel,* if extrinsic; *expel* or *correct,* if intrinsic), **destroy, neutralize,** or **antagonize** the causes of disease or **counteract** their effects. Whether any or all of these methods shall be attempted in a given case depends (1) on *knowledge* of the causative factors, (2) on the *nature* of the causative factors and their *relative importance,* (3) on the *time relations* of present phenomena to causative factors, (4) on *available means* of treatment.

Knowledge.—It is obvious that the more complete our knowledge of the causation of a given disease or affection, the more definite will be our methods of opposing it. In some instances, however,—notably n malaria before Laveran's discovery, and in syphilis and inflammatory rheumatism at the present day,—effective anticausative medication has been developed empirically.

The Nature and Relative Importance of the Causative Factors.—The part played by extrinsic agents, the part played by the organism tself, and the relative importance of the various factors, are often difficult to determine; but such determination is of the utmost benefit. Examples will best serve our purpose.

Acute disorders of the alimentary tract in children are often excited by infected milk; the withdrawal of milk from the diet diminishes the infective capacity of organisms within the alimentary tract, and by *avoidance* helps recovery.

Pulmonary tuberculosis is excited by Koch's bacillus in certain predisposed persons. The predisposition is, in my view, a preëxisting morbid condition, *i. e.*, a defect in vital energy having physical and chemical correlates in cell-constitution. This condition of 'hypotrophy' may have been inherited or it may have been acquired through privation, excess, or depression. Attempts to kill the bacillus or to neutralize its products have thus far proved abortive; but treatment directed to the correction of the intrinsic morbid conditions by reinvigoration of the patient, *i. e.*, to reinstatement of the vital resistance—is successful and, so far from being novel, its efficiency is attested by the records of centuries. The principle involved is *removal* (correction) *of the most important etiologic factor.* Withdrawal of a burning part from the fire; change of occupation in cases of occupational poisoning or neurosis; change of climate or other environmental factors in certain cases of asthma; excision of an infective sore; hypodermoclysis to stimulate diuresis or to dilute poisons; irrigation to wash away chemical irritants or bacteria; vomiting to get rid of toxic and irritative agents; evacuation of an abscess; expulsion of intestinal worms; elimination of intoxicants from the circulating juices by venesection, by sweating and similar measures—are other highly useful applications of the principle.

In cases of helminthiasis the use of vermifuges, of purgatives, and of irrigations illustrates *expulsion* of the offending agent; the particular species of the parasite determining whether or not its *destruction* be also attempted. In this connection the fact that a form of inveterate anemia, common in the Southern States of the Union, is now amenable to treatment directed against the cause (thymol to kill and expel hook-

worms), illustrates admirably both the relative importance of factors and the necessity of knowledge.

Malarial fever, already cited, depends on infection with Laveran's plasmodium. This can be *destroyed* with quinin, whereupon recovery takes place; future paroxysms being prevented.

Diphtheria depends on infection with the Klebs-Löffler bacillus, and after a certain period its chief manifestations are toxemic. Unlike tuberculosis, the predisposing conditions, important in prevention, cease to have significance after infection. At first, *destruction* of the bacillus *in situ* is possible, and may prevent intoxication; later, *neutralization* of the toxin is more readily effected than destruction of the bacillus. Moreover, it is possible to anticipate and *protect* against intoxication by the use of a neutralizing agent—*i. e.*, the antidiphtheric serum. We add, therefore, the use of the preventive and remedial antitoxic measure to the attempt at local destruction of the infective agent. In diphtheria, moreover, there is often an associated streptococcic infection, which has likewise to be dealt with topically and generally. So, too, in the case of other infectious diseases, the causative process is complicated, and we have to consider not only the pathogenic organism itself, but also its toxic products. In general it may be said that if the hostile organism does harm mechanically, by its presence, or if it sets up a local morbid process by chemical irritation, or if it appropriates to itself the nourishment of the tissues, the indication is for its removal, the inhibition of its growth, or its destruction; these objects being accomplished either *directly* by agents acting upon the micro-organisms (mechanical cleansers, antiseptics), or *indirectly* by agents acting upon the tissues to incite their defensive mechanisms or to render them an unfavorable culture medium. If the microbe does harm by setting up an intoxication, not only its removal, inhibition and destruction, but also neutralization and antagonism of the toxin and counteraction of toxic effects are indicated; and here, too, the action may be directly that of the remedial agent, or an indirect result brought about by biologic responses excited in the tissues. The intoxication set up by a pathogenic organism may not, however, be due to the chemical products which it elaborates, either offensively or defensively, but chiefly to its own substance liberated by its death. In a demonstrable instance, the indication for the destruction of the organism might no longer exist. The question would assume a quantitative aspect; and the etiologic indications might be confined to removal, inhibition, neutralization, physiologic antagonism and counteraction.

Antagonism may be illustrated by the use of certain drugs against

the toxic effects of each other in part or in whole; thus adrenalin and the nitrites antagonize each other's effect upon the blood-vessels; eserin causes the pupils to be contracted, atropin dilates them; strychnin and chloral have opposite effects upon nervous tissues. The action of the antagonists is directed toward the same tissue or function, opposingly. The etiologic use of organic extracts, as thyroid gland, thymus gland and the like, is in part based upon the principle of *antagonism*, in part upon that of *neutralization*. Other principles applicable in organotherapy are set forth elsewhere; we need greater knowledge to systematize this branch of therapeutic art.

In ptomain poisoning, vomiting and purging are natural reactions tending to *removal* of the offending material, but usually deficient; lavage and calomel are useful supplements; but if absorption has taken place and, hepatic neutralization failing, symptoms of collapse appear, it becomes necessary to *counteract* the effects of the poison by stimulation, the application of external heat, perhaps the use of strychnin. Counteraction based on etiology thus coincides with symptomatic counteraction, and an attempted distinction would be purely academic.

Time Relations.—French writers make a useful distinction between 'disease' and 'affection.' **"Disease,"** says Bouchard, "is the *ensemble* of the phenomena produced in an organism undergoing the action of a morbific cause and reacting against it." A special disease is a special train of such phenomena—a definite association of coexistences and sequences, depending on the action of a morbific cause and the reaction of the organism. Whether, therefore, we consider disease or diseases,* we are dealing with processes.

Affection is the *result* of disease. A tissue or organ is altered—affected—by some morbid process; and it may or may not return to its original condition with the cessation of that process. Familiar illustrations of the continuing results of disease that has ceased—usually termed *sequels*—are the affections of the heart-valves, remaining after recovery from acute infections, as rheumatism and scarlet fever; the strictures of canals remaining, or developing by contractions of cicatrices, after the subsidence of acute inflammatory processes, as in the urethra after gonorrhea or in the esophagus after deglutition of acids or alkalis. The pathogenetic agent having ceased to act, treatment

*I have elsewhere pointed out ("Disease and Recovery in Their Relation to Therapeutics," "Trans. Med. and Chir. Faculty," Baltimore, Md., 1896) that this use of the word 'disease' to denominate *the general state of ill health*, and of the word 'diseases' to denominate *special associations of phenomena of ill health*, is unfortunate and misleading; but English usage offers no alternative.

must be directed to the effect, not to the cause. In some instances, however, the cause continues to act, extending the affection, or exciting new affections. In malignant tumors this is probably the case, and both cause and effect demand attention. In syphilis our empiric anticausative treatment is applicable to a variety of manifestations long-continued, but not to the tissue degenerations properly denominated sequels—the parasyphilitic lesions. Likewise in the course of both acute and chronic diseases the question may arise as to the comparative importance, from a therapeutic viewpoint, of the etiologic factors and of the tissue-alterations (affections, lesions) and functional disturbances (symptoms) which they have produced. The time element will usually have considerable weight in such a decision. Any cause that has ceased to act can obviously be disregarded; but our question refers to continuing actions, as, for example, the uremic convulsions of nephritis, the cardiac distress of acute lobar pneumonia, the intestinal hemorrhage of typhoid fever. It is true that in many such special instances there has not yet been found an efficient agent to use against the cause of the tissue changes, or even against the tissue changes regarded as proximate causes of epiphenomena, as in the instance of uremia cited—but did we already have such in our possession, the time to depend upon it would have passed when the threatening phenomena had become manifest. They demand treatment from the pathologic or symptomatic viewpoint.

Available Means.—The best treatment in a given condition may theoretically be etiologic, but no agent that will fulfil the indications may be known, or, if known, at hand. We have as yet no dependable antitoxic or bacteriolytic serum against pneumonia. Antitetanic serum or antidiphtheric serum may not be procurable when needed. Venesection may be indicated to remove toxic matter from the blood, but circumstances preclude its performance. The physician must turn his thought elsewhere. The same considerations obviously apply to all other classes of therapeutic measures and elaboration is needless.

Pathologic-Therapeutic Diagnosis

In studying, for their therapeutic indications, the pathologic conditions present, past and probably to come, the importance of *knowledge*—or, to put it in another way, the hindrance of ignorance—is self-evident. It is to be remembered, however, that morbid anatomy does not constitute the whole of pathology; that the therapeutic nihilism which followed the establishment of the cellular pathology was based not on complete, but on imperfect knowledge; and that so long as we remain in ignorance of the atomic and molecular—the physical and chemical—

processes of cells, we cannot affirm upon any other than empiric grounds either the usefulness or the uselessness of measures of treatment designed to assist recovery of normal cell-composition and normal organic structure. A high degree of importance in this connection is assumed, moreover, by the studies of regeneration made by modern biologists. Death of individuals is a necessary part of the total phenomena of organic life; so death of cells is a necessary part of the life-phenomena of an individual organism. Disease induces premature degenerations of cells, which, if they proceed to destruction, may be followed by the casting-off of the dead tissue-elements and the regeneration of healthy ones. If, however, the impaired structural units continue in impaired life and reproduce in impaired kind, we have chronic organic disease—or, to follow the French terminology, affection. Hence the indication for therapeutic *destruction* and *removal.* This remedial hastening of cell-death is a procedure often carried out by the surgeon, but less frequently by the physician. Here, too, the question of *means available* arises. Radiotherapy promises to solve it for us in many cases.

A systematic and exhaustive study of the therapeutic relations of pathology would far outrun present limits. In the pathologic diagnosis preliminary to therapy we have to determine the character, extent, and effects of the morbid processes as affecting both structure and function. Thus we learn that we have to deal with congestion or inflammation; with ulceration or degeneration; with hypertrophy or atrophy; with active processes or with sequels (affections); with processes of increasing or of diminishing severity. We consider what dangers, if any, threaten or are present, as, for example, hemorrhage, effusion, suppuration, toxemia; and we determine what protective, eliminative, controlling, neutralizing, reparative, reconstructive and compensatory processes have been or may be instituted spontaneously, or can advantageously be aroused or imitated by art. We may thus decide to **protect,** as by antisepsis in surgery, as by rectal feeding in some cases of gastric ulcer, as by venesection when apoplexy seems imminent, as by rest to avert cardiovascular paralysis in acute pneumonia; to **remove** effusions or purulent collections or secondary toxic products (as in uremia or diabetes) by evacuation or absorption, or derivation; to **destroy** impaired cells or imperfect reconstructive tissue, so that the way may be cleared for effective regeneration or for better cicatricial reparation; to try to check the spread of inflammation or other morbid processes by external cold or other **antagonistic** measure; to **neutralize** chemical noxæ, as by alkaline infusion in the acid intoxication of diabetes; to **counteract** the ill effects of pathologic processes, as by trache-

otomy or intubation in laryngeal obstruction; as by the administration of aconite to oppose the excessive cardiac hypertrophy of mitral stenosis; as by venesection to relieve the overburdened heart and vessels; to **avert** incidental dangers, as by massage and electric applications to prevent the atrophy of unused muscles. **Recuperative** and **defensive** processes instituted by the organism being recognized, measures that will favor, aid and supplement them—or, being excessive or aberrant, measures that will control and regulate them—are sought. When defensive reactions, though ordinarily to be expected, are absent, one must seek the reason of the failure in order that the missing defense may be brought out, or, should this prove impossible, be substituted by some measure of art. Thus we put a febrile patient to bed, nourish to maintain strength, coaptate fractures, strap a pleuritic chest, apply poultices to hasten suppuration, check bleeding by facilitating the formation of clot, and so on. In morbid processes, moreover, to which natural defenses are commonly lacking, as in the flux and consequent algid condition of cholera,—in which the expulsive reaction, commonly defensive, has become morbid by excess and by pathogenic association,—one must recognize the situation, so that time be not lost in waiting, but the appropriate measures of *counteraction*—external heat, saline infusions, acids, opium, cocain, camphor, possibly suprarenalin, in the instance cited—be applied promptly. In brief, the pathologic-therapeutic diagnosis consists in an analysis of the entire series of events from inception to completion; the determination of their morbid or salutary tendencies; the estimation of the efficiency of the salutary reactions and of the importance of the morbid reactions. The most *available means* are then chosen with the view of checking or opposing morbid processes and of evoking, stimulating, assisting, or controlling recuperative processes.

Symptomatic-Therapeutic Diagnosis

Symptoms in the therapeutic diagnosis are considered in three main relations: (*a*) as *morbid* or *salutary* in themselves; (*b*) as indicative *individually* of certain pathologic states and processes; (*c*) as indicative *by their grouping* of certain definite associations of pathologic and etiologic phenomena.

First is to be considered the **immediate state** of the patient.

(A) Is there any condition present *directly threatening to life?*

If so, it demands precedence, and may even require action in advance of completeness of diagnosis. This is so obvious that no elaboration is necessary. Hemorrhage must be checked, suffocation relieved, cardiac

collapse averted. On the other hand, it should be equally obvious that even in the presence of threatening conditions, the greater one's understanding of the situation, the better guided will be one's action; and that to mistake uremic coma for apoplexy, hystero-epilepsy for tetanus, fracture of the skull for alcoholism, laryngismus stridulus for diphtheria, intussusception for impaction of feces, or pneumonia for appendicitis, may be a greater evil than to delay a little longer the institution of treatment.

(B) Is there *pain or functional distress* which, apart from any direct danger to life, is sufficient to call for relief? If so, is it of a character susceptible of mitigation except by treatment directed to the relief of the morbid complexus as a whole? Can it be relieved by measures that are either helpful to the general condition, or at least devoid of danger?

The importance of these considerations will best be shown by citing a few concrete examples. Obviously, if there be retention of urine and no counterindication is manifest, one need not complete one's diagnosis in order to advise drawing off the water. On the other hand, diagnosis is not altogether unimportant, for the probability of retention being caused by prostatic enlargement will guide the catheterizer in his manipulations. Pain in rheumatic joints may often be relieved by local applications, which are in any event harmless. Nevertheless our chief dependence is upon the specific treatment of the infection. The respiratory distress of acute lobar pneumonia may be mitigated by inhalations of oxygen, which are not only without detriment to the general condition, but of much benefit. The chest pain of the same disease may or may not yield to external applications of heat or cold; and then the thought will arise of using analgesic drugs—*i. e.*, opium, opium alkaloids, or some coal-tar product Knowledge of the general condition and its tendencies will, however, negative the suggestion. Nevertheless similar pain in uncomplicated pleurisy may safely be relieved with codein should rest, by strapping, be inapplicable or prove unsuccessful; and there are many conditions—for example, peritonitis, renal colic, inflammation of the frontal sinus—in which pain not only may, but must, be relieved by opium or morphin. Similar considerations apply to sleeplessness. Opium in some cases involves danger; in others it will act most kindly. The danger of inducing drug-habits must be considered in some cases, in others must be dismissed, in some must be risked because of the urgency of the situation. Following the guiding principle already set forth, we see that a harmless palliative measure may be instituted, when necessary, without delay, but that the use of

an agent capable of doing harm in any case must be preceded by a diagnosis as complete as possible.

Immediate conditions of urgency having been dealt with, it may be found that when the etiologic or pathologic indications are fulfilled, no purely symptomatic indication for intervention remains. Thus, when quinin has been given for malarial infection, or mercury for secondary syphilis, further treatment is usually a matter of nursing or of general prophylaxis. In a case of gastric ulcer, rest in bed with rectal feeding (perhaps, also, the administration of an alkaline salt, of a protective, as bismuth, or of an agent to hasten cicatrization, as silver) having been instituted,—or, on the other hand, operation having been done,—there commonly remains no more than careful, routine nursing. It is not always easy, however,—nor is it necessary in such cases,—to separate pathologic from symptomatic indications. The chief duty here lies in making sure that one is not misled into suppressing or obscuring, without good reason, symptoms—as pulse, temperature, respiration in acute fevers, pain in certain inflammatory conditions, cough in chronic pulmonary affections—whose natural evolution is necessary to keep the physician informed as to the progress of the disease in acute disturbances, and of the effect of the principal line of treatment in chronic ones; or into directing treatment by indications derived from symptoms of little consequence, to the neglect of the really important conditions. In some instances symptomatic—palliative or supporting—treatment must be instituted while waiting for the effect of measures based on etiology and pathology, or for the development of the natural defensive and recuperative processes. There are some cases, moreover, in which etiologic and pathologic indications are wanting or obscure, or in which means to fulfil them are unknown, imperfect, or unavailable. We are then compelled to depend wholly or chiefly upon symptoms for the therapeutic diagnosis. In any event, whether the therapeutic diagnosis be symptomatic merely, or whether it be based partly upon consideration of symptoms in themselves, and partly upon knowledge of the underlying pathologic processes and changes they indicate, it becomes a study of **disturbed function;** and can here best be elucidated from that viewpoint. We shall not, therefore, attempt an impossible refinement of study by excluding instances in which alterations of structure or definite morbid processes are known and considered.

Expectancy.—Concerning very many acute disturbances of function whether of known or unknown origin and pathology, experience has shown that they tend to subside promptly and spontaneously. This may indicate that the original morbid impulse has but little effect,

or that the cause does not continue to act beyond a limited time, or that the natural resistance and adjustment is sufficient. Obviously in such instances there is no call for therapeutic intervention beyond those simple precautionary measures that we speak of as good nursing,—the chief of which are rest, air, food and cleanliness. In other instances, however, the tendency to subsidence, while well marked, is not so prompt, nor is there surety of the absence of dangers during the process. In these, in the absence of definite indications or available means for causal treatment, most physicians adopt what is termed an *expectant* course. Rest, suitable feeding and good nursing generally, are instituted. The functional indications are then awaited, to be dealt with as they arise. The course of the disease may be definite, with gradual or sudden decline (lysis or crisis), or it may be indefinite and of irregular termination. In cases running a definite course, as typhoid fever and lobar pneumonia, the character of the manifestations to be looked for from day to day, the period at which definite dangers arise, the time at which to expect termination, are known, and the expectant plan can thus be conducted more intelligently than in cases of indefinite duration and irregular evolution, as catarrhal pneumonia, acute nephritis, or acute endocarditis.

Intelligent expectancy, always on the alert, fortified by knowledge of what to expect and of appropriate measures for **prevention** and **counteraction,** is the course best suited to the management of most of the acute infections, so long as we lack efficient specifics against their infective causes and toxic products. Expectancy, however, while it recognizes the natural defensive reaction and avoids unwise interference with symptoms, does not necessarily imply inaction. Thus, the systematic hydrotherapy (affusions, baths and water-drinking) that has so much reduced the mortality of typhoid fever is part of a well-planned expectant treatment and is directed toward the counteraction of functional disorders and attendant dangers, without the introduction of new and greater dangers. It is not antipyretic merely, but antifebrile; not only reducing temperature, but stimulating the natural reactive processes,—especially those of **elimination,**—reducing nervous disturbance, promoting circulatory equilibrium and conserving nutrition. It is supplemented by protective measures, the regulation of diet, the preliminary cleansing of the *primæ viæ* by calomel and the administration of appropriate intestinal disinfectants. Diarrhea, if troublesome, is combated—perhaps by alteration of diet, perhaps by lavage, perhaps by an astringent laxative, as castor oil, perhaps by astringent sedatives, as opium and bismuth. All in all, this is treatment by counteraction; but it exhibits also, as regards the special symptom, **avoidance** and **removal** of ex-

citants, and **supplementation** of an insufficient defensive reaction; **antagonism** not being resorted to except these have failed. Or it may be that constipation is the symptom requiring intervention, by change of diet, by high enemas of hot oil followed by colonic irrigation, even by the use of calomel or castor oil internally. Cardiac weakness may require attention; the precordial coil may suffice, or alcohol or strychnin may be called for. The dangers of hemorrhage and perforation are kept in mind. Symptoms suggesting such accidents are immediately investigated, and treatment, medicinal or surgical, instituted promptly, if necessary. Thus the course adopted, apart from the *protective* measures suggested by the knowledge of intestinal conditions, is based upon functional manifestations, is chiefly of the symptomatic order, and relies mainly upon *counteraction*. In acute lobar pneumonia the treatment is also largely expectant at present, but, again, not passively so. Venesection and saline infusion, so useful at the beginning of certain cases to remove and dilute toxins, are of *etiologic* indication. External heat and counterirritation, always applicable; venesection, sometimes useful in late stages for the relief of the overburdened heart; systematic cold sponging or cold bathing, sometimes indicated by excessive pyrexia or nervous disorder; aconite and veratrum viride, usually applicable in the inception to reduce or avert local congestion and inflammation; digitalis, nitroglycerin, strychnin, often useful in the progress of the case to sustain the heart or diminish its load; oxygen inhalations, that, fearlessly and freely used, may sustain life until crisis has safely passed despite the embarrassment of respiration, circulation and chemical interchanges—are based partially upon pathologic indications, partly upon well-attested empiricism. Whether to use or to withhold any or all of these or similar measures depends, however, upon the functional—that is to say, the symptomatic—indications in the particular case. Again, it is observed that the measures of expectancy fall chiefly under the head of agents of nutrition and of counteraction,—agents of support and of relief,—their purpose being (*a*) to prevent, to overcome, to balance, to compensate, the results of morbid changes in function and structure, and (*b*) to maintain the vital energy, so that the organism may be enabled to survive the evolution and termination of the disease. Especially is expectancy directed toward the known mechanism of death in the special affection—to avert, to oppose, to overcome. Knowing, moreover, the tendency of certain diseases toward complications,—as to nephritis in scarlet fever, to endocarditis and pericarditis in rheumatism,—the attempt is made to avert these, or, failing therein, to prevent them from causing death or passing into chronic affections. Should permanent im-

pairment nevertheless result, life being saved, may be made not only endurable but useful.

Expectancy, however, is not applicable in all cases of acute infection and intoxication. In autointoxications, as uremia and aceticuria; in most instances of drug-poisoning; in the fulminant (malignant or pernicious) forms of certain infections,—cerebrospinal fever, measles, smallpox, scarlet fever, malaria,—whether owing to unusual virulence of the germ or to abnormally low resistance of the patient; in diseases essentially fulminant, as thymic death and Asiatic cholera—organic reaction is itself perverted, or is absent, sluggish, or otherwise markedly deficient. As in wounds of large arteries, natural healing cannot be waited for. The physician may be able to accomplish little or nothing, but whatever is well to be done, is to be done quickly. If he can by any means remove or neutralize the poison or counteract its effects, nature may possibly take up the fight later, or, the fight being won by his intervention, nature has then simply to maintain life in such condition of complete or partial restoration as may have been achieved.

Relation of Chronicity to Treatment.—When functional disturbances tend to persist indefinitely,—that is to say, in chronic disorders or affections,—the expectant plan obviously ceases to be applicable. Natural processes of recovery or adaptation are evidently lacking, insufficient, inappropriate, or disproportionate; and therapeutic intervention is desirable. As a rule, etiologic indications are not present, unless we accept, as giving such, certain secondary causes more or less imperfectly recognized—as in gouty conditions and in diabetes. Pathologic indications may be clear or obscure; that is to say, the morbid anatomy or the pathologic chemistry may be known or wholly or partially unknown, or, if known, may be beyond correction by means available. In general, the nutritional and other functional indications are those of highest importance in the therapeutic diagnosis.

As a rule, the adaptive efforts of the organism are directed toward the maintenance of special function, despite impairment of structure, and toward the maintenance of function in general, despite the impairment of special function. The physician must be similarly guided. The natural and artificial compensations of valvular lesions of the heart offer the most striking and common illustrations. But processes, which, so far as known, nature does not compensate, are to be dealt with on similar lines. For example, in the chronic fibroid changes of blood-vessels, nerves, or viscera, while it would be highly desirable to find means by which integrity of structure could be restored, it would be idle to assert that we now have such means. We therefore endeavor

to maintain function in the damaged viscus or tissue and in the organism at large, notwithstanding the existence and perhaps the progression of the fibroid change. Thus, nitroglycerin, carbonated saline baths, massage, the gentle resistance exercises of the brothers Schott, are used to restore the balance of circulation, Turkish baths to promote elimination, and so on. Concomitantly, however, attention must be directed to the prevention of further changes: regulation of life, correction of diet, perhaps the use of arsenic, of mercury, of gold, of iodids, find application. Moreover, in accordance with the view of modern pathologists, that sclerosis of organs is frequently secondary to destruction of parenchymatous tissue, search is to be made for the cause of the parenchymatous lesion and its removal or neutralization attempted.

Treatment of chronic disorders and affections must necessarily be modified with the progress of the case, just as, in the expectant treatment of acute diseases, measures are chosen with reference to the existing stage of the morbid process and to the effect of previous treatment. It is to be observed, however, that progress is necessarily slow; that we do not, as a rule, aim to produce sudden changes or violent perturbations; and that hence the line of procedure, having been determined with due care, is to be persisted in long enough to demonstrate its worth. *Chronic cases necessitate chronic treatment;* in their management the physician must emulate that great general who, having deliberately and wisely planned his campaign, replied to objectors discouraged by apparent want of progress: "I'll fight it out on this line, if it takes all summer."

Chronic Disorders.—We have here to consider also persistent **disorders,** as neuralgia, gout, diabetes, hysteria and epilepsy, of which the etiology and fundamental pathology are obscure or unknown. To call them "toxemias" or "aberrations of metabolism" does not help very much—unless, like the good lady so comforted by the sound of "Mesopotamia," we find satisfaction in sonorous polysyllables. The purin-derivatives that act as proximate excitants of certain gouty manifestations can be dealt with,—by avoidance, by elimination, by neutralization,—but this treatment is only apparently etiologic. The cause of the aberrant cell-chemism is yet to be discovered, and, when found, it may prove irremediable. In diabetes, despite recent brilliant researches, our treatment is still directed against a symptom—the glycosuria—by control of which we seek to avert other symptoms; failing in which object, these symptoms may call for more direct palliation. Our methods are three: *avoidance* (of excessive glycogenesis), by restricted diet; *counteraction*, by the use of measures that restrain sugar

production or excretion or stimulate glycolytic processes in an unknown manner; and *secondary neutralization*, to avert the danger of acid toxemia by keeping the blood (and urine) alkaline, as already discussed under 'pathology.' Neuralgia, even though it occur acutely, exhibits so decided a tendency to recurrence that it is virtually a chronic disorder. We have to deal with one symptom—pain; we deal with it by *antagonism* or *counteraction*, and, failing this, by *destruction* of the affected nerve area. In hysteria we have only symptoms to deal with, but have developed as a *corrective* and *antagonistic* regimen an elaborate method of functional treatment, the *rest cure* and its adjuncts; employing likewise, as a measure of *secondary neutralization*, the suggestion of health as against the autosuggestion of disease. In epilepsy, apart from our *protective* hygienic régime, we can resort only to symptomatic *antagonism*, opposing convulsive tendencies by drugs that inhibit nerve-discharge.

Summary.—Symptoms indicate either processes or affections. Assuming the **processes** to have been recognized as salutary, as sufficient, and as proportionate, they obviously call for no interference. Assuming them to be salutary but deficient, they are to be aided or supplemented; salutary but excessive, to be restrained; salutary but disproportionate and irregular, to be controlled. Assuming them to be morbid, they may or may not call for opposition in accordance with the immediate damage or danger, their tendency to subside or to persist, and the probability of their causing affections, or of disappearing without trace. Thus, knowing that in a certain length of time the organic reaction will be sufficient to restore health, knowing that the immediate danger to life or the liability to impairment of function after termination of a morbid process, depends upon the action of a noxa upon a certain structure, or organ, or function, the physician may, in the absence of other threatening symptoms, ignore the general effects of the disease and concentrate his attention upon the maintenance of this special function or organ—for example, the heart in influenza; the kidneys in scarlatina. In general, distress is to be relieved, strength conserved, nutrition maintained.

Affections may or may not call for treatment in accordance with the character and severity of the symptoms to which they give rise. Thus in a given case of cardiac lesion so perfectly compensated that even upon exertion it gives rise to no symptom of functional disorder (rational signs), one may, perhaps, omit that regulation of the life of the patient which is usually advisable, and simply warn him against excessive activity. A slight degree of albuminuria persisting after an acute infection may not be accompanied by any symptom of imperfect

renal function, and may call simply for watching. On the whole, however, affections of sufficient degree to be discovered require at least hygienic management, to *protect* the patient against their extension or against possible evil consequences of imprudence. Counteraction is the chief means by which affections are functionally compensated. Their correction depends on pathologic indications.

Counteraction.—The principle of counteraction has frequently been alluded to, especially in connection with symptomatic or functional treatment. It differs from reaction, from antagonism and from neutralization, with each of which it is sometimes confused. A vital reaction is a response of the organism to excitation, extraneous or intrinsic. The reaction may be simple or complex, helpful or hurtful—or partially the one, partially the other. Antagonism, as we have seen, is manifested by opposing actions upon the same cells, tissues, organs or functions—calling forth opposing reactions. Neutralization is a mutually destructive effect of agents—psychic or material—upon each other, preventing either from influencing the organism. Counteraction opposes not the agent, the action, or the reaction, but the result of the last; sometimes mechanically or chemically, sometimes by the excitation of some other, and at times apparently unrelated, vital reaction. It is a principle of extended application and may be availed of by so many and so varied means and methods that it affords the largest scope for therapeutic resourcefulness.

Sneezing, turbinal turgescence, and outpouring of a watery secretion constitute a series of associated vital reactions to the contact of certain irritants with the Schneiderian membrane; usually helpful by the expulsion of the irritants and the prevention of their further penetration into the air-passages. Sometimes, however, these reactions become disproportionate in whole or in part and give rise to much distress, as in coryza and hay-fever. Nasal obstruction causes the mouth to be kept open instinctively, a reactive process that serves the purpose of a crude counteraction. The condition is not overcome, but its functional ill effect—deprivation of air—is averted. The same result may, however, be reached by antagonism, through the topical application of a vasoconstrictor, as cocain or adrenalin; or antagonistic treatment may be directed against the rhinorrhea by the use of atropin internally. Here the morbid conditions are overcome, although their cause is not opposed, and their pathology is unaffected. The disturbance of function due to shortening of a fractured femur is mechanically counteracted by the use of a thick-soled shoe. The functional result of esophageal obstruction would be starvation: it may be counteracted for a time by rectal

feeding or by gastrostomy. Intubation and tracheotomy counteract laryngeal obstruction. The use of acids and digestive ferments counteracts the organic or functional failure that diminishes quantitatively or qualitatively the gastric secretion. The action of digitalis upon the heart is in part antagonized by that of aconite; the action of atropin is in part antagonized by that of muscarin. The action of digitalis upon the heart may be utilized to counteract the effect of mitral regurgitation; that of atropin, to counteract in part the effect of aortic stenosis; that of aconite, to counteract in part the effect of mitral stenosis. Counteraction, therefore, whether considered etiologically, pathologically, or symptomatically, is principally a means of averting the functional results of processes and conditions that cannot be opposed directly. It does not directly remedy the condition whose effect it opposes; but by enabling function in general to be continued more efficiently, it aids in the maintenance of life and affords opportunity for natural adaptive or recuperative processes to be developed as far as possible; and for other measures of art to be directed toward changing for the better the morbid condition counteracted. Counteraction is not to be applied unintelligently or in a routine manner. The natural compensation is usually a mechanical or dynamic (reactive) result of the physical or chemical changes brought about by the affection counteracted. If, therefore, this natural stimulus be removed *in toto*, natural compensation will be prevented. On the other hand, insufficient compensation needs aid or supplement, and disproportionate or excessive effects of a compensatory order may demand restraint. The degree of counteraction to be attempted and the time for which it is to be continued are therefore matters of good judgment.

It is further to be observed that advancing knowledge may transfer some of our empiric-symptomatic counteractions to another order of expedients—as quinin is now seen to be an etiologic-destructive, and not a counteractive, agent in malaria; but symptomatic treatment usually implies either an absence of etiologic and pathologic knowledge, or the deliberate selection of other than etiologic and pathologic indications for treatment.

Therapeutic Modifications of Function.—In general, it will be found that symptomatic treatment is employed to heighten or to depress special functions—normal or disturbed—in order to *restore the general balance* of function. The function sought to be heightened may be one that is depressed or normal or insufficiently heightened; the function sought to be depressed may be one that is heightened, normal, or insufficiently depressed. This will depend on many circumstances.

A few illustrations must suffice. Depression of abnormally heightened function is sought through the use of bromids in epilepsy; of anodynes in neuralgia; of hydrotherapeutic measures in Graves's disease; of antispasmodics in asthma. Depression of normal function is sought when nitroglycerin is given to reduce vascular tension to the level of a dilated heart; and sometimes when venesection is employed to avert cerebral hemorrhage. Depression of an insufficiently depressed function is sought when aconite is used to slow the blood-current in a case of internal hemorrhage, or opium to check peristalsis in a case of peritonitis in which constipation already exists. Elevation of abnormally depressed function is sought when diuretics are given in cases of renal inactivity, when laxatives, massage, or electric applications are employed against constipation, when hematinics are given in anemia, when breathing exercises and pneumotherapy are resorted to in pulmonary tuberculosis. Elevation of normal function is sought by the administration of calcium chlorid to quicken clotting in hemoptysis; by diaphoretic and hydragogue measures in dropsies; by surgical procedures to establish collateral circulation in cirrhosis of the liver; by counterirritation and other derivative measures; by physical and mental diversion. Elevation of an insufficiently elevated function is sought when stimulating expectorants are used in acute or chronic bronchitis, when laxatives are given or irrigation is employed to empty the bowel in cholera infantum or dysentery.

Recapitulation

The clinical or symptomatic-therapeutic diagnosis includes, therefore, (1) the decision whether or not to intervene; (2) the determination of the purpose of intervention; (3) consideration of the immediate relief of urgent symptoms; (4) consideration of the necessity of counteraction, assistance, supplement, or control of symptoms in so far as these questions have not been determined by etiologic and pathologic indications; (5) determination of counteractive, auxiliary, or control method —whether by elevation or by depression of function, whether by direct or by indirect means; (6) choice of available means.

The general therapeutic diagnosis—etiologic-pathologic-symptomatic —is thus seen to represent the answer to five questions:

When (to intervene)?
Why (to intervene)?
Where (to intervene)?
How (to intervene)?
What (means to use)?

It is in helping the physician to answer the final question—what means of intervention to employ—that this system is intended to be especially useful; while the general and special discussions of principles, in connection with each method, and in the consideration of the practical applications of various methods in special conditions, will assist in the answer to each of the others.

THERAPEUTIC MEANS

It is evident, from our study thus far, that in choosing among the different means, physiologic and other, at command for application in a given case, one has first to discard the idea of sole, invariable and specific remedial measures save in the very few instances in which empirical or scientific observation has given us definite agents against definite infections. If we exclude from consideration intestinal parasites, it is probable that quinin against malaria, the specific antitoxins against diphtheria and tetanus, mercury and potassium iodid against syphilis,—perhaps salicylic acid against rheumatism,—will exhaust the list upon which there is virtual unanimity; and even of these diseases, exceptional cases stand out in which the specific agent seems to fail. Careful study must be made of the individual case, taking into consideration the "*ensemble* of phenomena" as well as the special phenomena; and not only from the viewpoints of etiology, pathology and functional disturbance, but also from that of the personality of the patient. Age, sex, race, heredity, occupation, temperament and the like are, it is true, included among etiologic factors, and may thus be said to have received consideration in the early stage of the diagnosis; but with the exception of occupation they are not subject to change; while only heredity and temperament may be antagonized or counteracted. In addition to these, there are numerous subtle elements going to make up the sum total of individuality, all of which must be reckoned with. The environment of the patient, physical and mental, is likewise to be considered. Its modification, or the substitution of an entirely different environment,—of climate, scene, work, play, persons, house, room,—may be most important. When, however, such change is impracticable, and, similarly, when the patient's means preclude the adoption of any other desirable measure, the facts are to be recognized and the physician's advice adapted to the situation.

Moreover, the physician must not lose sight of the fact that *his own personality* is a factor of no little weight. Not only his words, but his looks and his manner give suggestions of hope or of discouragement,

inspire confidence or arouse distrust. As to the words, let them be suitable and few; as to looks, let them be under control; as to bearing, let it be frank and natural, but at once cheerful and calmly assured. Forced cheeriness rings false, the assumption of solemn inscrutability repels the discerning, brusqueness is not the same thing as natural and hearty bluffness, and while its occasional necessity may be admitted, mostly it is as bad as the cloying sweetness of the 'that's-a-good-child' manner affected by some who have much to do with women and neurotics. Above all, the physician must dominate the situation. He may frankly admit ignorance or ask for time for greater assurance, when necessary—but his doubts are to be wrestled with silently; what he is to tell patients and friends must be his best and most certain judgment. He may at times withhold the truth, but he must not falsify. His directions are to be well considered, then given firmly, decisively, simply, clearly, and with sufficient, yet not excessive, particularity. Every physician can recall among his teachers the man of ideal personality—whose presence brought light and cheer into the sick-room, whose word was obeyed trustfully and promptly, who gave courage even when he could not bid to hope. Such are the examples for all to emulate.

To sum up: the rule which has been expressed, "treat the patient and not the name of the disease," might better be put thus: "*Treat the patient under the best possible environment, and to guide that treatment bear in mind all the facts, past, present, and to come, summarily indicated by the name of the disease.*"

Selection of Therapeutic Agents

Let us assume that, as the result of all the considerations necessary to be weighed in a given case, it has been decided to intervene therapeutically, at a time determined and for a definite purpose. As etiologic indications have already been sufficiently considered, let us assume that the purpose is to modify in a chosen direction a certain function. How is it to be accomplished?

In the last analysis, modifications of function depend upon the modifications produced in cell activity, and these, in turn, depend upon physico-chemical alterations in the constitution of the cells. Of the intimate nature of these processes we have scant knowledge and can form but the crudest image; for we can observe only gross results and have traced merely their coarser mechanisms. Nevertheless it is best to image the processes as best we can in the dim light of the facts that we possess. In the very general terms alone possible it may be said that the protoplasm of certain cells, or the soma as a whole, is irritated

in a definite way, evoking a definite response. The response is partly physico-chemical—that is to say, it can be explained by known physical and chemical laws; but it is conditioned likewise by that dominant energy for which as yet no satisfactory physical or chemical explanation has been given—the life-force, otherwise denominated formative force, vital energy, bathmism, or, as I have termed it, **bionergy.***

This statement, as we have had occasion to recognize in so many previous connections, holds good alike for morbific and for therapeutic agents. In so far as natural recovery as well as disease is part of a continuous response to their excitation, we have thus the apparent paradox that morbific agents are also the agents of recovery from their own ill effects. That paradox is still further illustrated when, to reawaken reparative processes that have come to a standstill, agents are used to provoke mild morbid processes,—as in irritant applications about old ulcers,—a measure based upon pathology; as in setons and fixation abscesses—measures based upon etiology and pathology, fanciful or real. The therapeutic effect depends on the excess of reparative energy called forth; and if we view recovery broadly as a biologic function,—a function of the soma,—the method appears identical with that spoken of, later in this discussion, as *concordant excitation by work to be done.*

Certain it is that no agent can be used in therapeutics that is not also possessed of morbific powers, and agents usually morbific may under certain circumstances be employed therapeutically or prophylactically. Whether a given agent shall be morbific or prophylactic or therapeutic depends upon the manner of its use in relation to the condition of the organism at the time of its use. Thus, chloroform or chloral may wisely be employed against the effects of strychnin poisoning or of tetanus, in quantities that would be lethal to the normal man. Quinin may be given with good result to malarial patients in doses that would probably produce amaurosis in the uninfected person. Mercury and iodids apparently destroy degenerated cells while still sparing normal ones. The radiant-activity destructive to cells of low organization is without such effect upon normal tissue. Such instances may crudely be conceived as neutralizations or antagonisms in which a certain portion of remedial drug or radiation is used up in opposing or destroying toxic drug or germ or degenerate cell. Drug effects or actinic effects

* Bionergy is assumed to be a phase of the universal energy, interconvertible with the other known and unknown forms of energy, but at the present stage of universal evolution and under existing terrestrial conditions educible from other forms of energy only by the activity of living-substance. It is thus conceived as self-perpetuating.

proper—physiologic or toxic—can be produced upon the soma or its normal parts only by the unneutralized excess. The problem is quantitative.

Moderate heat stimulates the activity and improves the nutrition of cells; great heat destroys them. Moderate cold stimulates, great cold destroys. Moderate light stimulates, excessive light destroys. X-rays stimulate or destroy according to their penetrative power and quantity; or if of given power and quantity, stimulate for a certain time, then destroy. Arsenic in sufficiently small doses stimulates certain forms of cell-activity; in larger doses, acts as a destructive agent. The same is true of cantharides and of many other drugs. Thus the difference between stimulation and destruction appears to be chiefly quantitative—a difference in degree of action constituting an apparent difference in kind. A crude comparison is afforded by the action of mechanical force upon a fly-wheel. Up to a certain point, the wheel revolves regularly and with accelerating speed; but excessive speed causes it to fly in pieces.

Cold applied to the surface of the body may diminish temperature by abstraction of heat—a purely physical result. It may also increase temperature by exciting a reactive heat-production—a physiologic effect. Both processes occur in every instance, but the duration and degree of one or the other result may be rendered relatively insignificant by the special method of the application. So, too, with reference to the action of heat and cold upon the vessels. There is a primary physiologic reaction against the application, causing constriction of vessels if cold be applied, dilatation in the case of heat; but this is quickly followed by a secondary—readjustive—reaction in an opposite direction. (See Volume IX, pages 21, 28, 36, 46.) Thus, the time and methods of application may be so varied as to produce opposite results with the same agent, and concordant results with opposite agents. The difference is again apparently quantitative. Underlying these various quantitative differences is probably a dynamic principle now becoming prominent in physical chemistry, and certainly of high importance in biology—the principle of critical equilibrium.

The effects of drugs and of physiologic measures on the healthy are not always good guides to their effects upon the sick. We have seen that such agents as quinin, when given in cases of malarial infection, and salicylic acid when given in rheumatism, are to a certain extent neutralized by the germ or poison of the disease, so that only the excess over the poison-saturation point is free to cause tinnitus or other overt manifestation of its presence. The curative action is apparently quite

apart from the influence of the drug upon the human organism. Similarly, digitalis often fails in certain febrile conditions to show its power over the pulse-rate. It has been suggested that digitalis neutralizes and is neutralized by pneumotoxin, only the excess exerting a clinical effect on circulation. Should this ingenious theory be confirmed by trustworthy experiment, the argument for large doses hitherto urged empirically would be placed on a scientific basis. It has been asserted that barium chlorid destroys or interferes with the action of the serum-complement (see page 29). Assuming the observation to be correct, the drug would be counterindicated in acute lobar pneumonia, despite the desirability, under certain symptomatic conditions, of its physiologic action upon heart and vessels. In other cases, it may be that drugs and other measures supposed to be useful in treatment by virtue of their so-called physiologic (normal function-modifying) effects owe their remedial power to properties of a different order. They may stimulate the production of protective substances or evoke other defensive reactions (*e. g.*, phagocytosis); they may supply the place of complement or amboceptor; they may interfere with the nutrition or the offensive and defensive chemism of microbes; they may be partially antitoxic—there is a wide field for speculation. The truth is that we are too much in ignorance of the chemical changes of disease in general and of special diseases, as well as of the effects upon cell-chemistry of our most used drugs and physiologic measures, to be even in a position to guess fairly at the reasons or mechanism of the varied phenomena, morbid, recuperative and therapeutic, that we observe, and by which in their large clinical aspects, we must, nevertheless, be guided. Basing ourselves as much as possible upon the facts of science—of physics, of chemistry, of general biology, of physiology, of pathology, of pharmacology—we are compelled in our final choice of therapeutic means to rely largely upon an intelligent, observant, rational and critical **empiricism.** It is to be remarked, however, that part of the great superiority of physiologic therapy over drug therapy lies in the fact that its measures are, on the whole, susceptible of better study and can therefore be applied with greater certainty.

Possibility of Influencing Structure

While the manner in which remedies act is not always clear, it is neither more nor less mysterious than any other fact of existence. Modern researches into the physical and chemical processes of life demonstrate that not only function but structure may be profoundly modified experimentally. By exposing meal-worms to the action of radium,

Danysz indefinitely retarded their development into moths; a process the opposite of that observed by Loeb and others, who have produced living larvæ from unimpregnated ova of sea-urchins under chemical change —according to Van't Hof, a change in osmotic pressure—in the surrounding saline medium.

If morbid alterations of structure in animals and men demonstrably follow the action of physical and chemical agents,—*e. g.*, heat, light, *x*-rays, acids, toxins,—it is not unreasonable to believe that remedial changes may be excited by the same classes of agents. Thus the disappearance of organic affections under therapeutic excitation of the organism would be no more wonderful than their appearance under morbific excitation, and would be equally in response to the fundamental laws of the organic structure. It is not a question of theoretic possibility, it is a question of the discovery of means. I am inclined to believe that such remedial changes take place more frequently than we have been willing to admit. From the very nature of the case, dead-house studies cannot determine the facts; but physicians who deal with observable lesions—the ophthalmologists, the laryngologists, the dermatologists—report recoveries which are in essence the restoration of structural integrity. I have observed what impressed me as similar recoveries from pathologic alterations of the viscera. Have not, indeed, the surgeons visually demonstrated such recovery in the case of peritoneal tuberculosis—and apparently from simple manipulation of the involved structures under exposure to light and air? The problem is simply one of an appropriate stimulus. The effect of a given stimulus must be determined *a posteriori*, and cannot in the present state of knowledge be asserted confidently *a priori*. An untried agent, chemically, mechanically, or electrically similar to one known to act by virtue of a definite chemical, mechanical, or electrical property may, however, be assumed to be likely to act in an analogous manner. The great advantage of physiologic methods over drugs in cases in which experience has shown the former to be applicable—their greater certainty of effect; the greater definiteness of knowledge as to the mechanism of the effect; the greater likeness of effects in health to effects in disease; the readier control of effect; the lesser liability of inducing a number of undesirable by-effects—thus receives further illustration.

Action of Therapeutic Measures

Therapeutic measures act in part upon cells, in part upon special organs and systems, in part upon the soma as a whole; in part upon

structure, in part upon function; in part upon body, in part upon mind. Their choice is necessarily governed by the character of the action desired.

In order to act **locally,** that is, upon certain cells or parts, we may have to take an agent that also acts upon certain other parts or upon all other parts. We prefer, however, to use one of restricted action if possible; thus, either an agent that may be applied topically or one to whose action the parts to be influenced will yield before the other parts are affected. On the other hand, when we desire to influence the body as a whole—that is, to induce a **general** action—we prefer an agent whose effects are similar throughout the organism; in other words, one that does not produce a series of effects in different parts tending to counteract or neutralize one another.

The measures of physiologic therapeutics admirably fulfil the requirements in both instances; being readily localized in action when necessary and being available with equal readiness for general effects of a concordant or synergistic character.

When the action desired is chiefly upon the **body,** physical and chemical agents are most appropriate, though psychic influence is sometimes useful. When the **mind** is to be affected, we may make use of any influence or agent that promises to produce directly or indirectly the kind of mental impression desired. Thus, harshness or gentleness, command, argument, or entreaty, prophecy disagreeable or pleasurable, electricity, mechanical vibration, medication, travel, regulation of diet and other expedients apparently equally incongruous from the ordinary viewpoint, are all, under given conditions, to be classed as psychic measures. It must not be supposed, however, that psychic measures are applicable only in cases of disordered mentality; or, on the other hand, that when mental aberration is the result of toxemia or of structural lesion of the brain, it is not to be considered and treated chiefly as a disease or affection of the physical man.

Modifications of **structure** are not often sought in normal parts; in morbidly affected parts they are commonly attempted by what are termed surgical means. Nevertheless, certain drugs—for example, iodin and its compounds—and many of the measures of physiologic therapeutics possess demonstrated utility in bringing about resorption of inflammatory products and destruction of morbidly altered cells, followed by reparation of healthy tissue. Nutritional measures, moreover, alter both qualitatively and quantitatively the structure of impaired parts, and among such may be those that act primarily upon function, as electricity and exercise in the case of wasting muscles. It is, however,

as we have seen in the study of the therapeutic diagnosis, chiefly toward the modification of **function** that the physician's intervention is directed —to elevate or to depress, to restore or to abolish, to modify in an unusual direction. We have already seen, too, that the agents which excite a given functional response (physiologic or toxic) in the normal organism may not act in the same way under the conditions of disease. Experience must be our principal dependence here. We can understand that when affection of the kidney has progressed to the destruction of most of the secreting structure, or myocardial degeneration has left but little functionating muscle, neither drugs nor physiologic measures can heighten indefinitely the action of the impaired organ; but it may need just that demonstration to inform us of the true condition.

Without attempting to elaborate this phase of the subject, but keeping it always in the background of our consciousness, the **methods** by which function can be modified may briefly be outlined.

Action upon function may be *direct* or *indirect*. Thus we may make use of agents that act directly upon the structure or nerve-supply of the organ to be affected—for example, digitalis upon the heart; or of agents that act upon the structure or nerve-supply of some other part—as, for example, when the kidney is stimulated through increase of blood-pressure brought about by action upon the heart and vessels, or when, through carbonated baths and gentle resistance exercises, the heart is relieved of a part of its load, thus making its normal functional stimulus more effective.

Whether direct or indirect, the action may be to *stimulate* or to *inhibit*. Stimulation carried to excess produces diminution, and finally cessation of function, through *exhaustion;* an effect never helpful, always harmful, and therefore to be guarded against. *Abolition of function* through sufficient inhibition may, however, be a legitimate therapeutic aim—as when local or general anesthesia is induced, when a pleuritic chest, a fractured limb, or an inflamed joint is immobilized, or when in cases of hemorrhage from the bowel in typhoid fever intestinal peristalsis is restrained by opium. Stimulation may also bring about a *modification* of function—as when the skin takes up vicarious elimination of urinary constituents. When function is completely absent, or so much depressed that it cannot for some time be excited to a useful point, and no vicarious stimulation is possible or useful, the attempt must be made permanently, or pending its reëstablishment, to supply by artificial means the factor necessary for vital equilibrium. When such means is lacking, death or great disablement cannot be averted. When such means is available,—as in artificial respiration, in the digestive ferments,

notably in thyroid and adrenal gland substance and similar agents of animal origin,—genuine therapeutic triumphs can be achieved.

Methods of affecting function may further be termed *concordant* or *oppositional*. They are *concordant* when they heighten the normal stimulus, increase the sensitiveness or force of the response, add to the available energy, or imitate the normal method of excitation; *oppositional*, when they lessen the normal stimulus, diminish the sensitiveness or force of the response, take away from the available energy, or reverse the normal method of excitation. The virtual effect of a concordant stimulus may likewise be brought about by measures that do not affect the function in question either directly or indirectly, but in some way oppose a morbific agent or its disturbing action.

There are two methods of imitating **normal excitation of function,** for which satisfactory descriptive terms are hard to find. One, which may be called *dynamic excitation*, is illustrated by the stimulation of muscular contraction, of sensation, or of secretion by electric applications, by vibratory massage, and by suggestion. The other—*excitation by resistance*, *i. e.*, stimulation by *weighting* or by *work to be done*—is illustrated by the effect of exercises with prisms upon the convergent power of the eye muscles, of food upon the digestive apparatus, of acids upon glands producing alkaline secretions, of muscular exercise upon the organs of circulation and respiration. Similarly *function is diminished* by *dynamic opposition*, of which certain anodal electric applications are instances; and by *substitution*—in other words, *unloading* or *relief from work*—variously illustrated by muscular and mental rest, by the use of blinders, and by the use of artificial digestants and predigested foods. The last-cited instance illustrates, moreover, a therapeutic danger—that agents used to supplement or substitute function may cause that function to dwindle or disappear through lack of exercise.

Concordant methods can be used only to heighten function, to stimulate. Certain organic functions may indeed be diminished by stimulating the normal inhibiting mechanism, but the mere statement of the fact in this manner brings out the true character of the action; while the paralysis of exhaustion, following overstimulation, is a morbific, not a therapeutic, effect. **Oppositional methods** are used chiefly to inhibit (diminish or abolish) function, but may produce a secondary excitation (*reactive stimulation*) that can sometimes be availed of therapeutically, being then virtually a concordant effect. Thus when a toxin is injected into a normal animal, it abolishes the function of certain cell-receptors; it is primarily oppositional. By a reaction that has found statement in a general biologic law, such loss stimulates the formation of new recep-

tors in excess; the secondary result is concordant. In hydrotherapy and other methods of utilizing temperature-effects we have also some of the best illustrations of oppositional stimulation. The excitation of heat-production by the application of cold, sometimes cited as such, is not, however, one of these. Like the heightening of muscular nutrition and power by exercise against resistance, it is an imitation—a systematization, perhaps—of the normal physiologic stimulus. Even when the prolonged application of cold results in a lowering of temperature, the effect, in so far as thermogenesis is concerned, is still concordant —of which fact shivering is a striking proof, being an evident attempt by muscular motion to increase heat-production. In such an instance we have to deal with a physical effect—heat abstraction—as well as with a physiologic reaction,—thermogenesis,—and the latter cannot keep pace with the former. It is to be observed, however, as a practical point of great importance, that in cases of abnormal thermogenesis (as in the pyrexia of typhoid fever) this physiologic reaction is not markedly excited until the temperature has been reduced below the point denoting the sufficiency of the recuperative response; and that its manifestation may be delayed for some hours, when heat will, like the antitoxic receptors, be found to have been produced in excess. Thus is brought about the hectic oscillation of temperature shown by the pump-handle temperature charts, when tubbing in typhoid fever is too frequent, too cold, or too prolonged; while, on the other hand, judicious bathing, just sufficient to overcome physically the excess of thermogenetic reaction,—a counteractive measure,—produces a temperature chart showing good control of fastigium and hastening of lysis, but preserving its characteristic—its normal—type. It is in the effect of hydriatric measures upon vessels that oppositional thermic stimulation is manifested The vascular dilatation following the contraction immediately ensuing on the application of cold—and, similarly, the constriction of vessels following primary relaxation on the application of heat, are genuine instances of *adjustments* (secondary reactions) *against* (primary) *reactions*, and are, therefore, illustrations of *stimulation by opposition*. Such oppositional or *paradoxic stimulation*, whether by drugs or physiologic measures, must in its primary application be brief or of minimum quantity, the effect depending, as already explained, upon the *excess* of the secondary reaction.

While morbid excitation must often be reduced by oppositional measures, as the convulsions of tetanus or strychnin by chloral, the overacting heart of sthenic pneumonia by aconite or veratrum viride, yet such expedients, however tempting, are always to be employed with

great caution; and in many cases are to be avoided altogether because of the dangers they involve. Thus in enterocolitis, the premature use of opium to check the apparently morbid excitation of the bowel may lock up poisons that, being absorbed, may increase illness and perhaps cause death; while cleansing of the intestine may be sufficient to diminish the stools to a number calling for no interference, or at least for no opium. More strikingly in fevers, the use of antipyretic drugs, apart from its undue interference with what is in large part a recuperative reaction, diminishes the vital energy, lessens resisting powers, lowers the defensive activity of the whole organism, and, while at best it can only mitigate a symptom, does so at the risk of determining death.

On the other hand, concordant measures rarely involve other risk —apart from the question of unwise interference—than that of weakening by overstimulation; a real risk, but one which a careful observer should not fear. And this brings into view the necessity for close observation of the effects of remedies; so that these may neither be confounded with the effects of disease—and thus both diagnosis and treatment go astray—nor be permitted to become excessive. As the dose of any remedy is: *enough* (to produce the effect desired) *and no more;* so the time for which its use should be continued is: *long enough and no longer.* The questions are all those of art, not of science; to answer them wisely demands careful watching and good judgment in the individual case.

The time required to pass in review the principal considerations that should govern the physician in his therapeutic diagnosis and his choice of therapeutic means has not been little, yet it could well have been made much longer by elaboration of many subjects briefly mentioned. Obviously no such time can be given to the formal consideration of every case at every interview with the patient. Needless or needlessly prolonged examinations are exhausting, and needless delay or prolixity in giving advice is depressing. Fortunately, after the principles have been mastered, they need remain only in the background of thought,—the subliminal consciousness,—informing and guiding the physician's quick decisions, which, apparently intuitive to the vulgar, are really the expression of long and painstaking conscious self-tuition. All progress is from the conscious to the automatic; so with muscular motion; so with the interpretation of sensations; so with much of the thought of students of the sciences and practitioners of the arts. The experienced and well-informed physician will adopt, through processes of thought virtually the same as those set forth in the foregoing pages,

but much apocopated in the actual, as simple a plan of treatment as possible. He will do nothing not clearly necessary; he will not hesitate to do all that is both necessary and possible. He will rather endeavor to overcome many disturbances with one method, than to use many methods to overcome one disturbance—yet he will wish to be informed of and to be able to use intelligently all promising agents. He will come to value highly all knowledge that increases his resourcefulness. He will seek to avoid deceiving either his patients or himself by attempts to achieve the impossible; yet he will be ever on the alert to push back further and further the line between can and cannot. To that end he must study faithfully and well the powers and the possibilities of all agents that may be utilized in his art.

The general reasons for preferring physiologic measures to the use of drugs when effective and available have been set forth in the Foreword to this System. The illustrations used in this discussion and the general references to auxiliary medication in nearly all the volumes show that the abandonment of drugs is neither advocated nor expected. Nevertheless there are very many cases in which physiologic measures will bring about recovery while drugs utterly fail, as, for example, in neurasthenia and hysteria. There are many cases in which both drugs and physiologic measures will assist recovery, but the latter are the more important, as, for example, in tuberculosis and in the infective fevers, especially typhoid. There are numerous cases in which drugs can be dispensed with entirely. There are a few cases in which drugs are as yet superior to any known physiologic measures; as notably in acute articular rheumatism, chorea, chlorosis, malaria and syphilis. In all cases drugs need to be supplemented by physiologic measures, if only those of nursing and diet.

In the discussion of natural recovery, and of the measures by which it may be favored, we have not overlooked, but neither have we emphasized, the facts that recovery is in very many instances partial and imperfect, and failure to recover is unfortunately too frequent. Death is the necessary termination of the individual organism, and death bringing to a close the period of natural senescence is not to be deprecated. It is premature death, premature disablement, against which the physician labors. When recovery is impossible, physiologic measures are often the most potent in relieving distress, in promoting comfort, in prolonging life.

The tendency of discovery, moreover, is to increase the means and enlarge the field of application of these measures. The Index-Digest, occupying so many pages of the present volume, renders it unnecessary

to cite special examples. They are there assembled in order and in demonstrative force. It may be permissible, however, to point out that they include most of the known measures fulfilling the etiologic indications, and very many of those fulfilling pathologic and functional indications; while even such important and urgent symptomatic indications as the relief of pain and sleeplessness may be fulfilled by these measures alone in very many instances, thus avoiding the induction of drug-habits.

Concerning **etiologic** indications, we find the general measures of prevention, and specifically the prophylactic serums; the climatic, aërotherapeutic, hygienic, gymnastic and nutritional measures generally; the eliminative measures, including venesection, saline infusion, various mineral and other baths, massage and exercise; the neutralizing measures, especially antitoxins and bacteriolysins.

Pathologic indications are fulfilled throughout a wide range by rest, exercise, hydrotherapy, massage, electricity, dietetics, pneumotherapy, climatic change, venesection, counterirritation, heat and cold, mental therapeutics, suggestion; while light and other forms of radiation promise to extend this class of applications still further. In **functional** and purely **symptomatic** treatment all the methods discussed are applicable.

The general principles that should govern the **selection** may fairly be stated thus:

When a physiologic measure will produce the result desired, it should be used in preference to any drug—thus, the drip-sheet or wet pack and massage rather than hypnotic drugs; cold water rather than antipyretic drugs; massage and electricity preferably to the constant use of laxatives.

When the result to be expected from a physiologic procedure is of slow development, drugs may be used meanwhile if needed, but should be discarded as soon as possible—thus, digitalis and nitroglycerin in some cases of heart disease submitted to Nauheim treatment, and palliative medication in cases of pulmonary tuberculosis treated physiologically. There is, however, no theoretic or practical objection to the continued use of drugs auxiliary to physiologic treatment, provided that such medication is useful and necessary.

When equally efficacious, measures not involving the use of apparatus or long journeys should be preferred—thus, baths at home over those at a spring or in an institution; respiratory exercises over pneumotherapy; massage over electricity.

When simple apparatus will suffice, elaborate apparatus is to be

avoided—thus, gasometers are to be used rather than pneumatic cabinets. Exceptions may be made, however, when legitimate and necessary suggestive effect is to be obtained from the more elaborate appliance.

When measures requiring elaborate apparatus or long journeys are, however, the ones needed or distinctly most efficient, they should be used without hesitation. Thus, an ocean voyage, a course at Nauheim, a sojourn at an altitude, or in a sanatorium, systematic hydrotherapy, baths, or inhalations of condensed and rarefied air, exposure to Roentgen-rays—may be the means of saving life, of hastening recovery, or of greatly promoting comfort, especially in chronic pulmonary, cardiac, metabolic, nervous, and cutaneous affections, and should not be neglected.

In **acute diseases,** rest, hydrotherapy, thermotherapy, aërotherapy, dietetics, serotherapy, offer the greater number of available measures. In **convalescence** from acute diseases, climate, light, massage, exercise, are added to the list. In **chronic affections,** diet, exercise, hydrotherapy, thermotherapy, electrotherapy, massage, aërotherapy, organotherapy, suggestion, are the most important.

In **affections of the digestive tract and of nutrition,** diet, water, mineral waters, exercise, massage, light, electricity, radiotherapy, organotherapy; in **affections of the circulatory system,** rest and exercise, baths, heat and cold, diet, pneumotherapy; in **affections of the respiratory tract,** pneumotherapy, inhalation, exercise, diet, hydrotherapy, light, radiotherapy; in **affections of the nervous system,** rest, hydrotherapy, electricity, exercise, massage, suggestion; in **affections of the skeleton,** rest, organotherapy, diet, manipulations, massage; in **affections of the muscles,** rest, exercise, massage, electricity; in **affections of the excretory organs,** water, massage, exercise, electricity, saline infusions, thermotherapy, organotherapy—fulfil the major indications.

For **stimulation,** radiotherapy, electricity, exercise, massage, thermotherapy, hydrotherapy, organotherapy, pneumotherapy, climate, suggestion, are employed. For **sedation,** rest, suggestion, massage, electricity, hydrotherapy, thermotherapy, are useful.

The great extent of the field of physiologic therapeutics is thus evident. Physicians who begin to apply its measures never abandon them, as so many drugs are abandoned, but rather enlarge their use. It is gratifying to believe that this system has contributed materially to such enlargement.

INDEX-DIGEST OF THERAPEUTIC MEASURES

ARRANGED UNDER HEADINGS OF MORBID CONDITIONS
AND REFERRING TO ALL THE VOLUMES OF THE SYSTEM

COMPILED UNDER THE SUPERVISION OF THE EDITOR

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INDEX-DIGEST OF THERAPEUTIC MEASURES

The object of this index-digest is to bring together for ready consultation, under the headings of the various morbid states and processes that can be benefited by the methods of physiologic therapy, an epitome of the measures applicable; so far as possible in brief index-style; with subclassification under the headings of the respective methods; and with references to volumes and pages where full discussion and description can be found. It thus serves the double purpose of a quick reminder of essentials and of an index to more detailed advice.

As many of the measures forming the principal topic of one volume of the series are alluded to in others, references to such allusions have been included whenever they seemed useful, whether for confirmation or further elaboration. The Roman numerals accompanying the various subheadings of methods indicate the volumes in which comparatively full discussions of principles or details are to be found—the principal volume standing first, the others following in parentheses. Thus under **"Tuberculosis, Pulmonary,"** will be found AIR, X (III, IV, V). This indicates that the special study of the utilization of air, modified or unmodified, in the treatment of tuberculous patients is to be found in Volume X, but that important references to the subject are also included in Volumes III and IV (on Climate) and in Volume V (on Prophylaxis and Hygiene). The page numbers are given in Arabic numerals under special items, and may refer to any specified volume. Thus, to continue the illustration of **"Tuberculosis, Pulmonary**—AIR," under the special item, **"Open-air treatment,"** will be found additional references not only to pages in Volumes X, III, IV, and V, but also to pages in Volumes VI (Diet), VII (Exercise), and IX (Hydrotherapy). As, however, these latter are allusions rather than discussions or descriptions, the volume numbers have not been given the prominence of general reference.

The references to such subjects as Baths, Climates, Health Resorts and Mineral Waters, while quite full, are not intended to be exhaustive.

If additional or special information is desired, it will be found in the index or text of the special volume dealing with the subject—thus, concerning Climates and Health Resorts in Volumes III and IV; concerning Baths and Mineral Waters in these volumes and also in Volume IX.

Certain morbid states and processes are necessarily referred to under a number of different headings, in accordance with the particular phase of disease or treatment considered in the portion of text to which reference is made, or its generality or particularity of statement. It has been deemed best in other instances to consolidate references under one heading. The cross-references given under such related heads as **Adhesions, Ankylosis, Articular Affections, Arthritis, Joints, Rheumatism,**—or **Bile-ducts, affections of, Calculi, biliary, Cholelithiasis, Gall-stones,**—illustrate both methods. If the particular information sought is not given under the heading first looked up, it will be found under one of the others indicated.

Immediately following the disease-name headings, references are given to any discussions of a general character that it has been deemed wise to indicate. After this, the various methods are given, so far as they pertain to the subject illustrated, in the following alphabetic order:

Air, Animal Extracts, Apparatus, Baths, Bloodletting, Climate, Corrective Manipulations, Counterirritation, Electricity, Exercise, Foods, Glasses, Health Resorts, Heat and Cold, Hygiene, Inhalation, Light, Massage, Medication (Auxiliary), Mineral Waters, Nursing, Prevention, Rest, Saline Infusions, Serums, Special Radiations, Suggestion, Water.

The following list of alternative designations of methods, legitimate and illegitimate, may assist the reader to find references desired:

Aërotherapy—see *Air*.
Aërothermotherapy—see *Heat* (*and Cold*).
Alimentation—see *Foods*.
Atomization—see *Inhalation*.
Balneology—see *Baths* and *Health Resorts*.
Christian Science—see *Suggestion*.
Climatotherapy—see *Climate* and *Health Resorts*.
Crounotherapy—see *Mineral Waters*.
Cupping—see *Bloodletting* and *Counterirritation*.
Diet—see *Foods* (also *Climate* and *Health Resorts*).
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Frigotherapy—see (*Heat and*) *Cold* (also *Air* and *Water*).
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Hill-climbing—see *Exercise* and *Health Resorts*.
Hot-air Cure—see *Heat* (*and Cold*) (also *Air*).
Hydropathy—see *Water* (also *Baths* and *Heat and Cold*).
Hydrotherapy—see *Water* (also *Baths* and *Heat and Cold*).
Hypnotism—see *Suggestion*.
Irrigations—see *Water* (also *Saline Infusions*).
Leeching—see *Bloodletting*.
Loutrotherapy—see *Baths*.
Magnetotherapy—see *Electricity* and *Suggestion*.
Mechanoneuraltherapy—see *Counterirritation* and *Massage*.
Mechanotherapy—see *Apparatus*, *Corrective Manipulations*, *Exercise*, and *Massage*.
Mesmerism—see *Suggestion*.
Mind Cure—see *Suggestion*.
Mountain-cure—see *Air*, *Climate* and *Health Resorts*.
Mystic Medicine—see *Suggestion*.
Nature-cures—see all headings.
Nauheim-cure—see *Baths* and *Exercise* (also *Climate*).
Oculotherapy—see *Exercise* and *Glasses*.
Ophthalmic therapy—see *Exercise* and *Glasses*.
Opotherapy—see *Animal Extracts* (also *Serums*).
Organotherapy—see *Animal Extracts* (also *Serums*).
Osteopathy—see *Massage* and *Corrective Manipulations*.
Phototherapy—see *Light*.
Physical Therapy—see all headings.
Pneumotherapy—see *Air* (also *Inhalation*).
Psychotherapy—see *Suggestion*.
Psychrotherapy—see (*Heat and*) *Cold* (also *Air* and *Water*).
Radiotherapy—see *Special Radiations* (also *Electricity* and *Light*).
Serotherapy—see *Serums* (also *Animal Extracts* and *Saline Infusions*).
Terrain-cur—see *Exercise* and *Health Resorts*.
Thermotherapy—see *Heat* (*and Cold*) (also *Air*, *Counterirritation*, and *Water*).
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Vibratotherapy—see *Electricity*, *Massage* and *Special Radiations*.
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cool half baths, the running foot bath, sural compress while the patient stands in water, 157; hot alcohol sponge, 529
See also under *Alcoho.ism, Hysteria, Melancholia, Neurasthenia*, etc.
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PREVENTION: care in food and water supply, V, 348
SALINE INFUSION: hypodermoclysis, IX, 292
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AIR: inspiration of condensed air, X, 269
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HEAT AND COLD: hot dry packs, IX, 143; sweat baths, 528
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wet packs, steam cabinet baths, cold shower baths, sitzbaths, and half baths, 143; lavage, colonic irrigation, 143, 280, 293, 295
See also under *Alcoholism, Arsenical Poisoning, Autointoxication, Cocainism, Mercurialism, Morphinism, Plumbism, Poisoning.*
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ANIMAL EXTRACTS: suprarenal, XI, 92
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application of a leech to the temple
COUNTERIRRITATION, XI, 189;
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IRRITATIVE SENSORY STATES
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JAUNDICE
CATARRHAL
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milk (small quantities and often), milk and lime water, peptonized milk, 261;
as acute symptoms subside, buttermilk, whey, broths of beef, chicken, mutton and clams, 261, 262; meat juice, raw eggs, 262;
later, milk toast, arrow-root, boiled rice, sweetbreads, oysters, meat jellies, fish, squab, scraped meat, and soft cooked eggs may be added, 262;
fats, starches, and sugars to be avoided, 262

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MINERAL WATERS, IV, 140, 349; **IX, 423, 481;**
alkaline acidulous: Bilin, Fachingen, Selters, and Gleichenberg, 481;
alkaline saline: warm, IX, 423;
alkaline, simple and **sulphated:** Carlsbad, Vichy, IV, 349;
muriated sulphur: Harrogate, Llandrindod, Bedford Sulphur Spring, Mt. Clemens, 349;
thermal: Carlsbad, Ems, Vichy, IX, 481;
suitable waters in the United States: Bedford Springs, Pennsylvania; Saratoga Springs, in New York; Greenbrier White Sulphur Springs and Irondale Springs, in West Virginia; Bedford Iron, Alum and Lithia Springs, Rockbridge Alum Springs and Bath Alum Springs, in Virginia; Bladon Springs, in Alabama, IX, 481; Indian Springs, Georgia, IV, 140
WATER, IX, 196;
enteroclysis in the form of high irrigation, twice or thrice daily, with fluid at a temperature of 53.6° to 62.6° F., in amounts of one or two quarts, 196; small retained enema of very cold fluid twice or thrice daily;
abdominal binder; cold sitzbaths
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FOODS: exclusive milk diet, VI, 262
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HEAT AND COLD: hot-air bath, local, IX, 275
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sand, hot: Ischia, III, 104; Koestritz, 218;
sulphurous, thermal: Aix-les-Bains, 186; Baden, 172; Barèges, 192
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HEAT AND COLD: hot air locally, IX, 271–275; X, 51; hot fir shavings, 381
LIGHT: incandescent electric light baths, IX, 124, 233, **238**
WATER: Scotch douches, IX, 89
EXUDATES IN
BATHS: lime: Bath, England; Budapest, Hungary; Ussat, France; Leuk, Switzerland; Hot Springs, Arkansas, etc., IX, 412; fango, mud, peat, III, 115, 182
ELECTRICITY: cataphoresis, II, 208
MASSAGE: local, VII, 63
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BATHS: salt: Bourbonne-les-Bains, III, 198; **hot-air,** IX, 271–275
WATER: local shock baths, IX, 529
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ELECTRICITY: faradic current or brush, II, 167; galvanic anode, 167; static, 167
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ELECTRICITY: electrolysis, II, 295
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KERATITIS, INTERSTITIAL
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ELECTRICITY: galvanic, II, 231.
MASSAGE: direct to the cornea, VIII, 391
SPECIAL RADIATIONS: *x*-ray, XI, 167, 170

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CONTRACTED; see *Nephritis, Chronic Interstitial.*
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COUNTERIRRITATION: dry cups, XI, 194
EXERCISE: Oertel method, VII, 163
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WATER: copious draughts of drinking-water, VI, 293

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LARYNGEAL IRRITATION
CLIMATE: African, Maritzburg, IV, 30

LARYNGISMUS STRIDULUS
INHALATION: amyl nitrite, X, 364; oxygen, 310
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atomization: ammonium chlorid, potassium bicarbonate, 425; suprarenal preparations, XI, 92
WATER: cold collar, IX, 96; cold throat compress, 523, 524; sweat bath, 528
CATARRHAL, CHRONIC
ELECTRICITY: mild galvanic current applied over the recurrent laryngeal nerve, II, 258
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ammonium chlorid vapor, 361; arsenic vapor, 380; carbonated arsenical waters, 432; ethyl iodid, 360; hydrogen sulphid, 331; iodin, 378; silver nitrate fumes, 381;
atomization: alum, 421; zinc sulphate and sulphocarbolate, 422;
insufflation: silver nitrate, 449
MINERAL WATERS:
alkaline muriated: Ems, Gleichenberg, Luhatschowitz;
saline chalybeate, mild: Rock Castle Springs, Kentucky;
sulphur: White Springs and Suwanee Springs, Florida, IX, 469
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INHALATION, X, 360, 384;
creasoted hot-water vapor, 384; ethyl iodid, 360; terebinthinated hot-water vapor, 384
TUBERCULOUS; see under *Tuberculosis.*
ULCERATIVE
FOODS, VI, 269, 270;
milk, broths, purées, eggs, soft custard, ice cream, weak tea and coffee, jellies, milk toast, oysters, scraped beef, 269;
feeding through an esophageal tube, 270; **rectal feeding,** 269
INHALATION: hot air, X, 47; insufflation, anesthesin, cocain, iodoform, morphin, orthoform, suprarenal, tannin, X, 449
MEDICATION (AUXILIARY): a 10 or 15 per cent. emulsion of orthoform in almond oil and yolk of egg injected into the larynx, VI, 269
See also under *Tuberculosis* and *Syphilis.*

LARYNGOBRONCHITIS
INHALATION: warm aqueous vapor medicated with compound tincture of benzoin and paregoric, X, 384

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INHALATION: atomization: opium, X, 425, 426; suprarenalin, XI, 93; tannic acid, X, 421
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EXERCISE (in moderation), VI, 246
FOODS, VI, 247;
milk, milk and egg, breast of squab and chicken, lean cold boiled ham, scraped or finely chopped beef, oysters, fish, stale bread, lettuce, spinach, boiled celery, green peas, oranges, stewed fruits, jellies, fruit juices, somatose;
inunctions of oil, 247
INHALATION: oxygen, X, 307
MEDICATION (AUXILIARY): arsenical preparations, VI, 246; laxatives, 247
REST: complete rest often necessary in severe cases, VI, 246
SERUM: leukolytic, XI, 65
SPECIAL RADIATIONS: *x*-ray, XI, 169; with fluorescent medication, 152
WATER: pure water to be taken freely, VI, 246
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SPECIAL RADIATIONS, XI, 152;
artificial fluorescence produced by administration of fluorescent substances and subsequent application of radium or *x*-ray
STOMATITIS IN
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only the blandest foods, such as milk, custards, gelatin, jellies, and arrow-root;
rectal feeding, 247
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LEUKORRHEA
BATHS: brine: Woodhall Spa, III, 286
CLIMATE: sea-air, III, 56
FERMENTS, XI, 109;
vaginal injections of brewers' yeast
MINERAL WATERS, IV, 131, 132;
chalybeate, sulphurous: Rockbridge Alum Springs, Sweet Chalybeate Springs, and Yellow Sulphur Springs in Virginia
WATER, IX, 75, 531, 534;
cold sitzbaths, 75; colonic irrigation, 531; vaginal irrigation, 534
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LIGATION OF ARTERIES
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EXERCISE: active, persistent, VII, 146
FOOD: regulated diet, VI, 350–355
HEAT AND COLD: hot-air bath, sweat bath, Turkish bath, IX, 267, 275, 528
LIGHT: electric light baths, IX, 238
MINERAL WATERS, IX, 422, 424, 427, 492;
alkaline, 492; Bonifaciusquelle of Salzschlirf, Assmannshausen, Sauerbrunnen of Radein; various lithia waters of United States; **simple sodium chlorid,** 427. Homburg, Kissingen, Harrogate, Saratoga, Lubec Saline Spring, 427; **warm alkaline saline:** Carlsbad, Bertrich, Geyser Spa, California; Castle Creek

LITHEMIA, MINERAL WATERS (*Continued*)
Hot Springs, Arizona, etc.; **cold sodium sulphate:** Franzensbad, Rohitsch, Elster, Gordon Springs, California; Harrodsburg, Kentucky, etc.
WATER: colonic irrigation, IX, 532, freely as a beverage
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LIVER
ABSCESS OF
ELECTRICITY: electric cautery, II, 220
AMYLOID DISEASE OF
MINERAL WATERS: alkaline thermal: Ems, Neuenahr, IX, 482
CIRRHOSIS OF
ANIMAL EXTRACTS: liver, XI, 119
FOODS, VI, 265, 266;
milk diet, 265; bouillon, soup, egg and milk, custards, Zwieback, small quantity of vegetables, 265; tea and coffee sweetened with saccharin, 266; string-beans, pears, mashed or baked potatoes, lettuce, tomatoes, chicory, carrots, turnips, spinach, salsify, artichokes, 266; starches and sugars to be avoided, 266; meats to be avoided as long as possible, 266; when their use is begun squab and chicken to be preferred, 266; condiments, rich sauces, fats, fried food, and pastry to be avoided, 266
HEAT AND COLD, IX, 250, 267, 482;
alternating hot and cold applications, IX, 250; warm peat cataplasms, 482; Turkish baths, 267
LIGHT: sun-bath, IX, 221
MINERAL WATERS: sodium chlorid waters containing bromin and iodin: Hall, Kreuznach, Krankenheil, IX, 482
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BATHS, IV, 348, 349;
muriated sulphur: Harrogate, Llandrindod, Bedford Sulphur Spring, Mt. Clemens, 349; **muriated thermal effervescent:** Nauheim, 348;
sulphated alkaline: Carlsbad, Vichy, 349
See also under *Water.*
MINERAL WATERS, IX, 423, 437, 480;
alkaline saline: Carlsbad, Marienbad, Kissingen and Homburg, etc., for vigorous persons, 480;
Franzensbad, Elster, Soden, Ems, and Gleichenberg, etc., for flabby, anemic persons, 480;
sulphurous: Eilsen, Meinburg, Gurnigel, French Lick Springs, Indiana; Grayson Springs, Kentucky; Avon Springs, New York; Cascade Springs, Tennessee, etc., 437;
warm alkaline saline: Carlsbad, Bertrich, Castle Creek; Hot Springs, Arizona; Geyser Spa, California; Manitou Springs, Colorado, etc., 423
WATER: abdominal binder, IX, 102; Turkish bath, 267; warm baths, 482

LOCOMOTOR ATAXIA; see *Tabes Dorsalis.*

LORDOSIS
EXERCISE: forward bending; chest-raising, seated; abdominal lifting, VII, 194 195; rod exercise, 177–180; 195–197
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LUMBAGO
APPARATUS: Zander's, VII, 136
BATHS: thermal springs, hot-air, mineral steam, steam, IV, 26; IX, 127, 267, 275, 408, 501
COUNTERIRRITATION, XI, 187, 194;
friction with any mildly irritating application; dry cupping, 194
ELECTRICITY: galvanofaradization, II 166
LIGHT: incandescent electric, IX, 239
MASSAGE: local, VII, 20, 45, 68, 70, 141; thermic, IX, 277
WATER: alternating hot and cold applications, IX, 172
See also under *Rheumatism, Muscular,* and *Myalgia.*

LUNG
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ELECTRICITY: electric cautery, II, 220
COLLAPSE OF
AIR, X, 102, 106, 262, 280, 281;
artificial respiration, 280; condensed-air bath, 102, 106; differential pressure methods, 262; indirect insufflation, 281–285
APPARATUS: bandages to the chest, VII, 102; chairs, corsets, etc., X, 277–280
EXERCISE: forced breathing, VII, 101; general gymnastics, X, 271; respiratory gymnastics, X, 273
LUNGS
CONGESTION OF
COUNTERIRRITATION: dry-cupping, XI, 194
INHALATION: amyl nitrite, X, 368
See also under *Congestion* and *Hyperemia.*
DISEASES OF; see under *Asthma, Bronchitis, Emphysema, Pneumonia, Tuberculosis, Pulmonary.*
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HEAT AND COLD: sweat baths, IX, 528
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LUPUS ERYTHEMATOSUS
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MEDICATION (AUXILIARY): iodoform, II, 295
SPECIAL RADIATIONS: *x*-ray, II, 295; XI, 167
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ELECTRICITY: electric cautery, II, 296
HEAT AND COLD: local application of hot air, IX, 48
LIGHT: electric light, IX, 54, 230; actinic rays, 225
SPECIAL RADIATIONS, II, 211, 296; XI, 139, 140, 152, 167;
x-ray, II, 211, 296; XI, 167; artificial fluorescence produced by the administration of fluorescent substances and the subsequent application of radium or the *x*-ray, XI, 152
LUXATIONS
BATHS: peat and mud; acratothermal; thermal brine (used after luxations), IX, 501
EXERCISE: exercises and resisted movements directed to the muscles and fascia of the joint involved, VII, 68
HEAT AND COLD: superheated air, VII, 68
INHALATION: nitrous oxid, VIII, 68
MASSAGE: local, VII, 67, 68; short and frequent applications, 20
LYMPHATISM
INHALATION: oxygen, X, 307
WATER: hot compresses, IX, 68

MADURA FOOT
PREVENTION: disinfection of discharges, protection of hands and feet, disinfection of wounds, early operation when the disease develops, V, 301
MALARIA
FOODS: liquid diet: milk, gruels, broths, orange-juice, grape-juice, lemonade; generous diet, rich in meats, during convalescence
INHALATION, oxygen, X, 308
PREVENTION: destruction of mosquitos and their breeding-places, avoidance of malarial regions, prophylactic doses of quinin, V, 309
WATER: cold vigorous shower baths, cold rub, sheet baths, cold sitzbaths of ten minutes' duration, cold full baths, plunge baths, cold fan douche, IX, 136
CHRONIC
CLIMATE: resorts at high altitudes, IV, 207
HEALTH RESORTS, (III), IV, 123, 137, **298;**

MALARIA, CHRONIC, HEALTH RESORTS (*Continued*)
St. Moritz, Ceresole Reale, Auvergne Mountains, the Riviera, Appalachian Mountains, Rocky Mountains, Pacific Coast Range, seaside resorts of New England, Virginia, and Southern California, IV, 298; Morgantown, N. C., 137; Glen Summit, Pa., 123
MEDICATION (AUXILIARY): arsenic, quinin, IV, 297
MINERAL WATERS, III, 194; IV, 296, 297, 298; **IX, 446, 456;**
arsenical iron: IX, 446;
muriated alkaline, thermal: La Bourboule, III, 194;
sulphated alkaline: Carlsbad, Franzensbad, Tarasp, IV, 296;
sulphated iron: Alexisbad, Levico, Mitterbad, Muskau, Parad, Ratzes, Roncegno, Ronneby, Serebrenica, IX, 456;
sulphated muriated: Brides-les-Bains, IV, 297;
sulphur and chalybeate, thermal: Virginia, California, 298

MALARIAL CACHEXIA
MINERAL WATERS, IV, 298; **IX, 445, 446;**
arsenical iron, IV, 298: Wildbad-Gastein, La Bourboule, Tarasp, Val Sinestra, Levic, Lausigk, Thompson's Bromin-Arsenic Springs, etc.;
sulphated iron, 445: Mitterbad, Parad, Ronneby, Tuffier, Sharon Chalybeate Spring, N. Y., Bath Alum Spring, Virginia, etc.;
sulphur and chalybeate, thermal: Virginia and California, IV, 298
WATER: sweat baths, IX, 137
See also under *Anemia* and *Chlorosis*. See also under *Malaria, Chronic.*

MALIASMUS; see *Glanders.*

MALIGNANT PUSTULE; see *Anthrax.*

MALNUTRITION
ANIMAL EXTRACTS: lecithin, XI, 111; thymus, XI, 86
COUNTERIRRITATION: digital manipulation, XI, 196
See also under *Anemia* and *Debility.*

MANIA, ACUTE
FOODS: full feeding, milk, VIII, 207
MASSAGE: daily, unless it increases excitement, VIII, 207
MEDICATION (AUXILIARY): VIII, 207–210;
calomel, followed by a saline, 207; paraldehyde, whisky, trional, sulphonal, 208, 209; iron, strychnin, arsenic, bitter tonics, 210; scopolamin, hyoscin hydrobromate, 208
REST: complete or partial, VIII, 207
WATER: warm sponge bath, warm pack, prolonged hot immersion baths, VIII, 208

MARASMUS
ANIMAL EXTRACTS: thymus, XI, 86; lecithin, 111
FOOD: nutritious, easily assimilated, oil inunctions, VI, 166, 199
See also under *Tuberculosis.*

MEASLES
FOODS: milk, broths, gruels, lemonade, grape juice, fruit juices, VI, 196
INHALATION: nitrogen monoxid, X, 337; oxygen, 308
NURSING, V, 486, 514, 515
PREVENTION: isolation of the sick, disinfection of discharges, anointing the body during period of desquamation, V, 239, 286
WATER: warm or hot baths, IX, 525; warm compresses, 139; moderately cool half baths of five minutes' duration, 139; cold affusions, 139; momentary immersion in cold water, followed by vigorous friction, 139; trunk compresses, wet packs, 139
GERMAN. *Treatment practically as above.*

MELANCHOLIA
ANIMAL EXTRACTS: thyroid, VIII, 206; XI, 82
EXERCISE: passive, Swedish movements, VII, 55; (VIII)
FOODS: milk, eggs, forcible feeding, VIII, 199
HEALTH RESORTS, IV, 90, 92, 162;

MELANCHOLIA, HEALTH RESORTS (*Continued*)
Kennebunkport, 90; southeastern coast of Massachusetts, 92; Ashland, Bayfield and La Pointe, Wisconsin, 162
MASSAGE, VIII, 198
MEDICATION (AUXILIARY): placebos, hyoscin, scopolamin, paraldehyde, trional, sulphonal, chloralamid, bromids, opium, VIII 202; iron, arsenic, 203
NURSING, V, 493
REST: relative, prolonged in bed, VIII, 197
SUGGESTION: amusement and occupation, VIII, 257
WATER: sponge bath, VIII, 198; Turkish bath, IX, 266

MENINGES, IRRITATION OF
COUNTERIRRITATION: blisters, XI, 189; digital, 196
HEAT AND COLD: cold to head and spine, heat to extremities, IX, 72, 95, 257
WATER, IX, 72, 75, 89, 169;
filiform douche, 89; hand baths and foot baths, 72; cold head compresses, cold applications to the nape of the neck and vertebral column, 169; sitzbath, 75

MENINGITIS
CEREBROSPINAL
COUNTERIRRITATION: blisters, XI, 189
FOODS: milk, gruels, broths, kumiss, custards; **rectal** or **stomach-tube feeding; during convalescence:** eggs, cream toast, cereals, scraped or minced meat, oysters, chicken, fish, jellies, fruits, bread and simple vegetables, VI, 210
PREVENTION (OF EPIDEMIC): isolation of sick, destruction of discharges, V, 277, 515
WATER: very hot baths of ten minutes' duration; cold applications to the head, nape of the neck and vertebral column, IX, 169
CHRONIC
ELECTRICITY: galvanism and faradism, II, 180

MENOPAUSE; see under *Climacteric.*

MENORRHAGIA
ANIMAL EXTRACTS: mammary, XI, 106; suprarenal, 93; stagnin, 102
BATHS, IV, 361; IX, 496;
cold steel baths, peat baths, IX, 496; brine baths, IV, 361; thermal gaseous muriated baths of Nauheim, 361
CLIMATE: high altitudes, IV, 361
HEAT AND COLD, IX, 205, 535;
bits of ice in the vagina, vaginal injections of ice water, 205; hot vaginal injections, 205, 535
MASSAGE: local, VII, 75
MINERAL WATERS, IV, 361; IX, 496;
muriated, muriated alkaline, sulphated, IV, 361; sodium chlorid, cold, IX, 496
WATER, IX, 205, 535;
cold shower baths, cold rubs, cold sitzbaths of short duration, 205; hot and cold vaginal injections, 535

MENOSTASIS
WATER: cold sitzbaths, IX, 75

MENSTRUAL DISORDERS
ANIMAL EXTRACTS: mammary, XI, 106; ovarian, 105; thymus, 83, 86; thyroid, 83
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tea, coffee, cocoa, alcohol, acid fruits, starchy vegetables and sweets are counterindicated, 347;
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Western Riviera, Egypt, Lakewood, New Jersey; Hot Springs, Virginia; Santa Barbara and Redlands, California, are winter resorts suitable for convalescence, 287
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absolute rest, 496; confinement to bed for at least one week after the temperature has reached normal, 489
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sulphur: Richfield Springs, N. Y.; Mt. Clemens, Michigan, 349
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HEAT AND COLD: local application of hot mud, IV, 288; local hot-air bath, IX, 275 (IV)
LIGHT: local electric light bath, IV, 288; IX, 233
MASSAGE: local, IV, 288
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SMALLPOX
FERMENTS: brewers' yeast, XI, 109
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rectal feeding;
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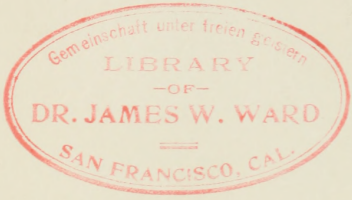

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